Perinatal Psychopharmacology

Faruk Uguz
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Editors

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Preface

Non-psychotic mental disorders are amongst the most common morbidities in pregnancy and postpartum (together referring to the *perinatal period*). So far, research about mental disorders in the perinatal period has largely focused on depression, particularly postpartum depression, even though increasing evidence shows a substantial morbidity with other psychiatric disorders such as anxiety disorders, obsessive-compulsive disorders, eating disorders, bipolar and schizophrenia spectrum disorders. Furthermore, recently available evidence from literature underlines the importance to consider both antepartum and postpartum period as equally particularly vulnerable and risky for pregnant and nursing women's mental health.

In the last decade, there have been a growing number of evidence-based publications in the field of *perinatal psychiatry*, some focusing on the risk of an untreated psychiatric disorder for the mother and foetus or infant, others on the efficacy and safety of the available treatments, including psychotropic drugs. Individualised risk/benefit analyses are needed when judging the use of a drug treatment in the perinatal period, as evidence for the risks of such drugs is largely based on observational studies, which makes it difficult to clearly establish a causal relationship. However, for some psychotropic drugs (e.g. benzodiazepines, some antidepressants and mood stabilisers), no contraindication exists for their use in pregnancy as the risk of severe untreated maternal anxiety and/or affective disorders is far greater than the risk of adverse complications derived from such medications.

The present book provides an evidence-based overview of data coming from the latest clinical studies, reviews and meta-analyses, focusing on the efficacy and safety of perinatal psychopharmacology.

The four chapters of ***Part I*** focus on the epidemiology, maternal and infant drug metabolism, pharmacokinetics and pharmacodynamics of psychotropic drugs during pregnancy and breastfeeding, an overview of the most commonly used safety parameters and risk categories used in perinatal psychopharmacology and a comprehensive summary about the general approach to perinatal psychopharmacology in terms of benefit/risk balance, risk factors for mothers and foetus/newborns. In ***Part II***, eight chapters summarise the most relevant clinical information on the neonatal safety of psychotropic drugs (for each class), both during the pregnant and postpartum (lactation) period, particularly focussing on the risk of congenital malformations, miscarriages, gestational and perinatal complications, neurocognitive and behavioural development of newborn. ***Part III*** focuses on the pharmacological

management of psychiatric disorders during the perinatal period, including the risks related to untreated maternal disorders during pregnancy and postpartum period. At the end of each chapter in ***Part III***, a complete summary of clinical recommendations (i.e. ***Expert recommendations***) has been included for clinicians' decision-making.

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Part I

Introduction to Perinatal Psychopharmacology

Epidemiology of the Use of Psychotropic Drugs in Pregnant and Nursing Women

1

Sura Alwan and Anick Bérard

1.1 Introduction

Psychiatric disorders include a wide range of illnesses that are usually chronic and relapsing during an individual's life-span. The most commonly encountered psychiatric disorders include depression, bipolar affective disorder, schizophrenia, obsessive-compulsive disorder, and anxiety disorders. Women of reproductive age are more likely to develop some of these common conditions and can be specifically vulnerable when they are affected in the perinatal period, defined as "including the entire period of pregnancy, the periconception period and up to 12 months postpartum." A recent UK analysis has reported that 25% of women aged 20–35 years who commit suicide do so in the perinatal period and that these women were twice as likely to have been receiving mental health care mostly with regard to anxiety and depression illnesses [1].

Pregnancy is believed to be neither protective against mental illness nor a specifically high-risk period. There appears to be no significant differences in the rate of psychiatric and mood disorders between pregnant and nonpregnant women of reproductive age [2]. Few studies, however, report on the impact of pregnancy on severe mental and psychiatric conditions [3]. Bipolar disorder has been most studied in this regard, and it appears that its overall recurrence risk in the perinatal period can exceed 70% [4]. Furthermore, untreated maternal, mental, and psychiatric illness in pregnancy is related to several factors and unhealthy lifestyle habits that could negatively impact pregnancy outcome, such as poor nutrition, smoking, alcohol drinking,

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illicit drug use, as well as other maternal conditions including diabetes [5–7]. There is also evidence in the literature that maternal mental illness itself, including stress and other psychiatric conditions, could be associated with adverse pregnancy outcomes such as congenital malformations [8, 9], spontaneous abortions [10], prematurity, low birth weight, NICU admission, and operative delivery [3, 10–13].

Besides the risk of the untreated illnesses, pharmacotherapy of these disorders is further complicated by concerns over potential risks to the pregnant woman and her prenatally exposed or breastfeeding infant, including structural and behavioral teratogenicity, neonatal toxicity, and other adverse reproductive outcomes. The absence of randomized control trials (RCTs) in this field, due to the difficulty and ethical concerns of conducting them during pregnancy, results in most safety and/or risk data being extrapolated from observational studies of pregnancy outcomes, which need to be interpreted carefully because of their specific limitations and biases. For example, in a qualitative study based in the UK to understand the perspectives of women with psychiatric illness and the process of decision-making about the use of psychotropic medications in pregnancy, most women expressed the view that healthcare professionals had access to limited information on which to base their recommendations, creating at times an interactional difficulty in the healthcare professional-patient relationship at a critical time and leaving women to rely on their common sense and experience to base their own decisions [14].

Fortunately, however, the advent of online computer-based clinical teratology knowledge bases, such as *TERIS* (http://depts.washington.edu/~terisweb/teris/index.html) and *REPROTOX* (http://www.reprotox.org), has greatly simplified the process of collecting and analyzing the available information and translating into proper clinical assessment of human teratogenic risk through careful interpretation of data from several kinds of studies on these medications. In addition, pharmaceutical labels that are now developed in accordance with the revised US Food and Drug Administration (FDA) Pregnancy and Lactation Labeling Rule (PLLR) provide clinicians a narrative up-to-date summary guide for communicating risk to their patients [15, 16]. Furthermore, within the past three decades, the development of teratogen information services (TIS) in North America (https://www.mothertobaby.org), Europe, and around the world (~~https://www.entis-org.eu/~~) has greatly improved the access of pregnant women and their healthcare providers to available information over the telephone (and sometimes through text messaging) and have fostered a systematic approach to risk assessment and risk management [17, 18]. TIS centers have been unique in combining multidisciplinary expertise representing teratology, dysmorphology, toxicology, pharmacology, epidemiology, clinical genetics, obstetric medicine, infectious disease, and occupational health in order to understand the potential for a specific agent to interfere with normal embryonic or fetal development [19].

1.2 Psychopharmacology in Pregnancy and Breastfeeding

Management of mental and psychiatric illnesses in the perinatal period is challenging and becomes more difficult when the pregnancy is unplanned, which is the case in nearly half of pregnancies [20]. Therefore, it is important that healthcare

providers discuss pharmacological risks of pregnancy at the time of administration for all women of reproductive age as well as alternative treatment options such as psychotherapy. Psychotropic medications in pregnancy are prescribed for women who develop moderate to severe psychiatric disease while pregnant or undergo a relapse or exacerbation of their pre-existing disease during pregnancy [21, 22]. It is estimated that at least one in ten women is prescribed with a psychotropic medication in the perinatal period [23]. However, there remains limited information available in the literature on the patterns of the use of many of these agents among women in the perinatal period, specifically on how these rates may have changed over the past decade, over different geographical regions, and over the course of a pregnancy, with the increasing evidence-based data and warnings from regulatory bodies.

1.2.1 Antidepressants

Depression affects about 20% of women of childbearing age [24], and up to 15% of women report depressive symptoms during pregnancy [25]. Untreated maternal depression during pregnancy is the strongest predictor of postpartum depression [26, 27] and is associated with inadequate self-care and poor compliance with perinatal care [10, 13].

The increasing use of antidepressants over the past two decades, specifically with regard to the selective serotonin reuptake inhibitors (SSRIs), has put these medications among the most common therapeutic prescriptions worldwide. In the USA, for example, the National Center for Health Statistics reports that between 2011 and 2014, antidepressants were the first most commonly prescribed class of medications among females (13.9%) and the second most commonly prescribed therapeutic class of medications for both genders (10.7%) following antihyperlipidemic agents [28].

Rates of exposure to an antidepressant at some point during pregnancy have ranged between 2% and 10% [29–35], with the lowest rates reported in Scandinavian populations, while the highest rates reported in the US population. The increase in antidepressant use in the perinatal period over time has also been established worldwide. A Danish population-based study reported a 16-fold increase in the use of an antidepressant at some point during pregnancy, where the exposure rate increased from 0.2% in 1997 to 3.2% in 2010 [33]. A fourfold increase in antidepressant prescribed during pregnancy has been reported in the UK between 1992 and 2006 [36]. Similarly, in the USA, reports of antidepressant use in pregnancy have shown increases from around 1.5% in 1996 to 8.1% in 2005 [29, 30, 32, 37]. In the USA, dispensing of an antidepressant medication during pregnancy was more common among older women, non-Hispanic White race, women living in the Midwest, and those with higher education (>12 years) [29, 32, 37]. Other reported predictors of antidepressant use in the perinatal period were periconceptional smoking or alcohol use and having comorbid disorders, such as prepregnancy type 1 or 2 diabetes and hypertension [29]. Similar patterns of use and predictors have also been described for Canada and Europe [33, 38].

During the course of a pregnancy, a sudden decrease in the use of an antidepressant, regardless of the type, was observed in many studies around the third month of conception, which appears to be related to the time at which pregnancy was recognized and may indicate the possibility of healthcare providers being reluctant to continue treatment after the occurrence of pregnancy [29, 34, 35, 37, 38]. However, the attempt to decrease the fetal risk of antidepressant use during pregnancy by discontinuing treatment in women with severe depression has been associated with increased risk of relapse of the depression with its associated adverse pregnancy outcomes [26].

1.2.1.1 Selective Serotonin Reuptake Inhibitors

SSRIs account for about 80% of all antidepressant prescriptions and are being prescribed for a variety of conditions, other than depression [39]. Fluoxetine (Prozac®) was the first introduced SSRI in 1988 and became the most frequently prescribed antidepressant worldwide [40]. Other SSRIs currently available on the market include citalopram (Celexa®), escitalopram (Lexapro®), fluvoxamine (Luvox®), paroxetine (Paxil®), and sertraline (Zoloft®). SSRIs share a similar mechanism of action by blocking the reuptake of serotonin (5-HT) via the serotonin transporter (SERT). However, each SSRI differs from another with regard to its chemical structure and pharmacokinetic properties [41] and therefore has the potential to affect the developing fetus in various ways. Given that the majority of antidepressant use during early pregnancy, the period of organogenesis, is due to inadvertent exposure, when women do not know that they are pregnant, SERT site blocking, by SSRI intake when cells are non-differentiated, may potentially result in a variety of malformations.

Maternal SSRI use in pregnancy has gained considerable clinical attention over the past decade. Many studies of the effects of maternal treatment with an SSRI on development of the fetus and child have been reported. These included risk of organ-specific birth defects, and of heart defects specifically, with first-trimester exposure to SSRIs [31, 42–46]; risk of neonatal withdrawal syndrome [47–51]; persistent pulmonary hypertension of the newborn (PPHN) [52–55]; prematurity, low birth weight, and small-for-gestational-age infants associated with late-pregnancy exposure to SSRIs [56–58]; as well as an increased risk of autism spectrum disorders (ASD) and other neurodevelopmental disorders in children who were prenatally exposed to SSRIs [59–63]. There remains a debate, however, on how much of these adverse effects are actually related to the medications versus the underlying illness itself and/or related comorbidities, lifestyle, and other risk factors. Regardless of the actual cause, the US FDA has issued a public health advisory in December 2005 regarding the potential risk for cardiac defects in relation to first-trimester exposure to paroxetine as a result of two preliminary reports published at the time. This was followed by another FDA health advisory warning in July 2006 stating an increased risk of PPHN among infants prenatally exposed to an SSRI in the second half of pregnancy. These warnings have affected the pattern of the use of SSRIs during pregnancy, with the rate of paroxetine use in pregnancy dropping significantly in North America. Interestingly, however, paroxetine is reported to be the most

frequently dispensed SSRI to women in the perinatal period in Italy and the Netherlands, with no reduction in its use following the US FDA warnings [64].

In the USA, where prescriptions of SSRIs have the highest frequency, sertraline was reported to be the most frequently prescribed SSRI among pregnant women [29, 37], while in European countries, citalopram in Scandinavian countries [33, 65] and fluoxetine in the UK [66] have been reported to be the most commonly used SSRIs in the perinatal period. Prescription of SSRIs also varies by different geographical regions within the perinatal period. For example, in a European pharmacoepidemiologic study based on six electronic healthcare databases [64], at least 40% of women with a prescription to an SSRI during the year before pregnancy discontinued use before pregnancy and did not restart the medication during the year following delivery. Continuing treatment with an SSRI throughout pregnancy and following delivery was more common among women in Denmark and the Netherlands compared to those living in Italy, with the lowest rates.

In terms of breastfeeding, SSRIs vary in the degree to how much they cross into breast milk, but sertraline and paroxetine appear to be most tolerated by nursing babies than other SSRIs [67]. However, most studies regarding the safety of antidepressants in breastfeeding are confounded by prenatal exposure to the same drug, which may increase the risk of early adverse effects, as well as other lifestyle risk factors, including smoking and alcohol and substance abuse, and no studies exist on the long-term cognitive and behavioral development on the breastfed children.

1.2.1.2 Bupropion

Bupropion is an aminoketone that is structurally and chemically different from other antidepressants on the market. It is a weak inhibitor of neuronal uptake of dopamine, norepinephrine, and serotonin and does not inhibit monoamine oxidase [68]. It was first marketed as an oral antidepressant (Wellbutrin®) and was subsequently developed as a non-nicotine aid to smoking cessation (Zyban®). Because women who smoke are encouraged to stop doing so when they become pregnant [69], it is therefore not surprising that many women are treated with bupropion in early pregnancy [70]. Regardless of the indication for use, bupropion is the second most commonly used non-SSRI antidepressant in the perinatal period, with a reported frequency of 0.7–1.0% among pregnant women in the USA [23, 29]. There is very limited data on the use of bupropion perinatally in other parts of the world. Available data on the safety of bupropion in human pregnancy is also limited. Some studies have reported a slight increase in the rate of congenital heart defects, in particular, left ventricular outflow obstruction defects following bupropion use in early pregnancy [71–73], but the absolute risk was estimated at 2.1–2.8 per 1000 births.

1.2.1.3 Other Less Commonly Used Antidepressants

Tricyclic antidepressants (TCAs) were once the treatment of choice for depression and panic disorder before the introduction of SSRIs. They remain commonly used for comorbid conditions and when treatment with an SSRI has failed. About 0.2% of women are exposed to a TCA sometime during their pregnancy [23, 29], and some neonatal withdrawal symptoms have been reported with their use in late

pregnancy [74]. The most commonly used TCA is amitriptyline, which has a mechanism of action similar to SSRIs with regard to the blocking of SERT. Recently, Berard et al. [43] have shown that amitriptyline use during gestation was associated with an increased risk of birth defects, and that its use during late pregnancy could increase the risk for the child to develop attention deficit with or without hyperactivity disorder (ADHD) [75].

Selective norepinephrine reuptake inhibitors (SNRIs) are the most recently introduced class of antidepressants, and they work in a similar mechanism to SSRIs, but they also block the reuptake of the neurotransmitter norepinephrine along with serotonin in the brain to help relieve depression and are also commonly prescribed for other conditions, including anxiety disorders and long-term chronic pain. SNRIs are increasingly being used in pregnancy with an overall reported frequency of up to 0.8% based on a US population [23]. Venlafaxine (Effexor XR®) has been the most frequently used SNRI in pregnancy and lactation, with earlier small studies reporting on its safety in pregnancy [76, 77] but larger more recent studies indicating possible associations of its use in early pregnancy with birth defects and spontaneous abortions [43, 78].

1.2.2 Anxiolytics

Anxiety constitutes the most common mental disorder among women of reproductive age and specifically women in the perinatal period. In fact, it appears to be that among women taking antidepressant medications in pregnancy, anxiety diagnoses are nearly as common as depressive diagnoses, and antidepressant users with an anxiety disorder are twice as many as antidepressant users with a depression disorder [23]. Even though there is evidence in the literature that maternal stress and anxiety in the perinatal period can negatively affect both mother and baby [12], women's concerns of the risk of medications in pregnancy and their overestimation of drugs' teratogenic risk may lead to low adherence and discontinuation of needed therapy upon recognition of pregnancy. Nevertheless, antianxiety medications, or anxiolytics, are the second most commonly used medications in the perinatal period after antidepressants. Anxiolytics include benzodiazepine and benzodiazepine-like medications. A few studies have looked into patterns of the use of anxiolytics in the perinatal period, and in one US study, the rate of the use of benzodiazepines and benzodiazepine-like medications was estimated at 3.9% in pregnancy, with zolpidem (Ambien®) being the most common one dispensed among pregnant women (2.4%) followed by alprazolam (Xanax®) (0.8%) [23]. Diazepine (Valium®) use in pregnancy was much lower at 0.6%, and only 0.05% refilled more than one prescription for it in pregnancy, which is probably related to its association with the cleft lip and palate in the infant in earlier reports that have not been confirmed in several later studies and reviews [79]. Although data are limited with long-term effects of these medications, associations with neonatal withdrawal symptoms have been reported in prenatally exposed and lactating infants [80].

1.2.3 Antipsychotics

The use of antipsychotic medications is indicated for a number of conditions, including psychosis, schizophrenia, and bipolar disorder. However, the use of antipsychotics has increased over the past two decades, partly because the approved indications for these agents have expanded beyond these conditions to also include depression, obsessive-compulsive disorder, anxiety disorders, and autism spectrum disorders [81, 82]. Apparently, as many as 25% of patients with depression and up to 50% of patients with bipolar disorder also have psychotic symptoms [22]. The rate of antipsychotic medication use during pregnancy has also increased over time [83], and their use in pregnancy constitutes an important clinical issue because of the concern over their risk to the fetus. Reported adverse outcomes of prenatal antipsychotic use include congenital malformations, preterm birth, small for gestational age [84, 85], as well as short-term delay in development and lower neuromotor performance [86, 87].

Confounding by indication could not be ruled out in the observed increased rates of adverse outcomes. Schizophrenia is best studied in pregnancy, and the untreated condition appears to be associated with low birth weight, small-for-gestational-age infants, and preterm delivery [88]. It is important to note that schizophrenia patients are more likely to have unplanned pregnancies along with associations to certain lifestyle factors, including lower educational levels, higher body mass indices (BMI), smoking and alcohol use, and lower adherence to multivitamin use [89], all of which may contribute to an increased risk of adverse pregnancy outcomes. Furthermore, since psychosis interferes with commitment with prenatal care and parenting, it is believed that risks of not managing schizophrenia outweigh risks of managing it therapeutically. However, indications for the use of both first-generation and second-generation antipsychotics include depression in more than 50% of cases, followed by bipolar disorder and schizophrenia [83].

1.2.3.1 First-Generation Antipsychotics (FGAs)

The neuroleptic FGAs, also known as the typical antipsychotics, were the first antipsychotic treatment of choice for psychiatric disorders. These medications act through blocking dopamine receptors in the dopaminergic pathways of the brain, as excessive dopamine release is associated with psychotic experiences. The most commonly used agents of this class in the general population and among women in the perinatal period are chlorpromazine (Thorazine®) and haloperidol (Haldol®). Because they have been available longer in the market, they have a better history of use in pregnancy and an established safety record as monotherapy, specifically with regard to haloperidol [90]. However, in over a 10-year period between 2001 and 2010, the rate of the use of FGA drugs during pregnancy in the US population has remained constant at 0.1% [91], which is probably due to the more frequent use of atypical antipsychotics among women of reproductive age. Over the course of a pregnancy, the prevalence of FGA use is reported highest in the first trimester and then drops by the second and third trimesters [83].

Limited data is available on the safety of typical FGAs for breastfed infants, but data on haloperidol have been reassuring, with no reported adverse effects [90].

1.2.3.2 Second-Generation Antipsychotics (SGAs)

Although the first atypical antipsychotic, clozapine (Clozaril®), was introduced in the 1960s and was widely used since then, a number of SGA agents were subsequently introduced in the past two decades and have received approval for various indications, including irritability in autism, mood stabilization in bipolar disorder, and additional therapy for major depression, all of which are conditions which have been marked with notable increase in the rate of their diagnoses. As a result, the prevalence of the use of SGA in general significantly increased among the general population and has also been evident among women in the perinatal period. For example, a threefold increase in the rate of the use of SGA among pregnant women in the USA, from 0.4% to 1.3% over a 10-year period, has been reported [91], with the most frequently reported SGAs being quetiapine (Seroquel®) and aripiprazole (Abilify®). Polytherapy with other antipsychotics and antidepressants is reported in more than half of pregnant women on an SGA, and about 25% of them also take a mood stabilizer or a benzodiazepine simultaneously. In Europe, the prevalence of women on antipsychotic medications in general is lower and ranges between 0.1% and 0.3% [92, 93]. About 50% of women discontinue therapy with an SGA upon recognition of pregnancy, while 60–70% stop taking an SGA by the third trimester of pregnancy, and among those who switch medication at the beginning of pregnancy, the majority are reported to switch to quetiapine [91]. It is not surprising that quetiapine is reported most commonly among women in the perinatal period as it has a wide range of off-label indications, as well as its established safety profile in the literature with evidence showing a lower placental transfer compared to other antipsychotics [94]. Quetiapine is also recommended the most for lactating women with low concentrations of the drug found in breastmilk.

1.2.4 Mood Stabilizers

There has been an increase in bipolar disorder diagnoses among women in the perinatal period, which is consistent with the increase observed in the general population, possibly due to improved classification of people who were previously misdiagnosed as having unipolar depression or, on the other hand, overdiagnosis of this condition. Whether treated or untreated during pregnancy, bipolar disorder may increase the risk for preterm birth, Cesarean and instrumental delivery, and other adverse outcomes [95].

Mood stabilizers that are used to treat bipolar disorder include lithium and antiepileptic drugs, most commonly, carbamazepine and valproate. Lithium is the only medication with established evidence in meeting all criteria for the treatment of bipolar affective disorder, through ameliorating and preventing recurrences of both mania and depression [22]. Lithium use in early pregnancy has been associated with an increased risk of a congenital heart defect known as Ebstein anomaly, which is a serious malformation that involves redundant tricuspid valve tissue with downward

displacement into the right ventricle. Although the risk for this malformation was overestimated earlier, recent literature suggests that the rate is much lower than previously reported (1 in 4000) [96].

Both valproic acid and carbamazepine are contraindicated in pregnancy because of their association with high rates of malformations and other adverse outcomes, including long-term neurodevelopmental disorders [97]. On the contrary, both medications are considered for breastfeeding because of their low serum levels in breast milk, but close monitoring has been recommended [98]. Lithium is not recommended for breastfeeding mothers because of the risk of its accumulation while the neonatal kidney is still immature.

1.2.5 Stimulants

The use of stimulants increased from 0.4% to 0.9% during pregnancy between 2007 and 2011, possibly due to increased diagnoses of attention deficit hyperactivity disorder (ADHD) in adult women [23]. There remains very sparse data available on exposure to stimulants during pregnancy and lactation, and many women opt for discontinuation of stimulants upon recognition of pregnancy because of lack of knowledge on their safety.

1.3 Conclusion

Whenever pharmacotherapy is indicated for a pregnant or breastfeeding woman with a psychiatric condition, the risk of medication exposure to the infant must be weighed against the risks of untreated maternal illness. However, confounding by indication has been a common methodological limitation in many studies affecting both treatment decisions and outcomes, especially when many women are affected by more than one mental health disorder and are taking more than one psychotropic medication. Given the high prescription rates of psychotropic medications and the broadening of indications for their use among women of reproductive age, there is an urgent need to clarify their associated risks or confirm safety of their use in this critical period, in order to help patients and their healthcare providers start proper preconception planning and make informed treatment decisions during the course of pregnancy and postpartum.

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2 Maternal and Infant Pharmacokinetics of Psychotropic Medications During Pregnancy and Lactation

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2.1 Pharmacokinetics of Pregnancy

Pregnant women often take over-the-counter, herbal, or prescribed medications, and there is a trend for increased medication consumption by pregnant women over the last decades. Moreover, pregnancy and the postpartum period are now clearly recognized as a risk situation for the development or exacerbation of many psychiatric disorders, increasing the possibility that a pregnant woman will require a pharmacological treatment involving a psychotropic medication. However, there is limited evidence regarding the safe use of medications during pregnancy and lactation. From a pharmacokinetic perspective, only few studies focus on the physiological changes that take place during pregnancy, and even fewer attempt to link pharmacokinetics to pharmacodynamics. Unfortunately, despite the growing need, there is modest incentive from the industry to invest in improving our knowledge about the pharmacokinetics and pharmacodynamics of psychotropics during pregnancy and the lactating period [1, 2].

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2.1.1 Pharmacokinetics of the Pregnant Woman

Dynamic changes in the female physiology during pregnancy affect several pharmacokinetic parameters and further amplify the already present sex differences in drug absorption, distribution, metabolism, and elimination of psychotropics, especially when interacting with the altered hormonal milieu [3, 4]. Such complex changes often result in counteracting effects, which creates difficulties in the assessment of their net effect on drug pharmacokinetics. Pregnancy decelerates women's gastric emptying, as well as the small bowel and colonic transit time of the drug. Therefore, drug absorption is generally decreased [5]. However, in some cases genetic polymorphisms of the P-glycoprotein (Pgp) may lead to a reduced transport activity and thus higher plasma drug concentrations [6]. During gestation, there is an escalation of the maternal plasma volume, which reaches a 50% increase during the third semester. The protein-binding capacity of the drugs undergoes changes, albumin levels are lowered, and the ratio of lean muscle to adipose tissue is decreased. Moreover, the free fraction of drugs is increased. Most psychotropic drugs have a lipophilic profile and show a greater volume of distribution during pregnancy, which may lead to lower peak plasma concentrations [5, 7, 8]. Due to a simultaneous higher clearance, the plasma concentration of drugs is often lower than in healthy adults [9]. As gestation progresses, the renal blood flow and the glomerular filtration rate (GFR) are increased, and this results in acceleration of drug elimination. Although data is still inconclusive, hepatic blood flow seems to increase as well, leading to high drug extraction ratios [5, 7, 9].

Nevertheless, the most complex and pronounced changes in the pharmacokinetics of psychotropic medications during pregnancy are due to the hormonal induction or inhibition of metabolic processes. Both the cytochrome P450 (CYP) family, which plays a key role in the phase 1 drug metabolism, and the phase 2 metabolism enzymes, such as uridine diphosphate glucuronosyltransferase (UGT) and n-acetyltransferase, are modulated by sex hormones during the gestation period. CYP3A4, which is already more active in female than male adults, is further induced during gestation due to progesterone. Sex hormones also induce CYP2A6 and CYP2D6 and increase glucuronidation by upregulating UGT1A4 and possibly UGT2B7. On the other hand, CYP1A2 and CYP2C19 are inhibited by increased levels of sex steroids during pregnancy. During the late stages of gestation, the activity of CYP1A2 is reduced by 65–70%, and CYP2C19 activity is reduced by 50% in comparison to the postpartum period. However, it is important to mention that the maternal metabolic phenotype (poor, intermediate, extensive, or ultrarapid) plays a key role in the final metabolic rate, and that, for every enzyme phenotype, the metabolic rate is affected at a different extent. Therefore, many drugs require close and personalized dose monitoring during pregnancy [5, 7]. Moreover, drug plasma concentration may increase in women with a poor metabolizer genotype and, as a result, more of the drug is transferred to the fetus through the placenta [6].

After delivery, sex hormone levels in the maternal plasma decrease rapidly, and during the postpartum period, the plasma volume is normalized, and the hepatic enzyme activity returns to baseline after a short period of time. There is also a

decrease in the renal blood flow and glomerular filtration rate, which also return to normal range. Thus, after delivery, this rapid normalization of previously modified factors may lead to high drug maternal plasma concentrations, especially if the drug dose administered during pregnancy is not closely monitored and modified during the postpartum period [5].

2.1.2 Pharmacokinetics of the Fetus and the Neonate

The modified maternal drug pharmacokinetics, in combination with the placental transfer potential and the fetal drug metabolic rate, determine the fetal psychotropic drug exposure [5]. Fetal exposure depends on the drug dose, the maternal absorption, distribution, and elimination, the placental transfer and the fetal distribution and elimination of the drug. Three main factors determine the drug's placental transfer rate: the lipophilicity of the drug, the pH gradient across the placenta, and the drug's protein-binding characteristics.

It is known that nonionized, low molecular weight, lipid-soluble drugs are well absorbed. The concentration of a lipophilic drug tends to reach an equilibrium across the two sides of the placental barrier, and therefore the rate of drug transfer is largely dependent upon the concentration gradient (indicated by the fetal/maternal ratio) and the placental blood flow [9]. Most psychotropic drugs administered to pregnant women are highly lipophilic, cross the placental barrier, and reach and distribute to the fetal compartment with varying transfer rates, possibly causing teratogenic effects, neonatal toxicity, withdrawal syndromes, or long-term neurobehavioral effects [6–9]. After delivery, the previous equilibrium between the fetus and its mother via the placenta does not apply to the neonate. For this reason, high concentrations of a particular drug in the fetus may result in significantly prolonged effects postnatally [9].

Another determinant of placental crossing of psychotropic drugs is their affinity for drug transporters. Transplacental passage is moderated by these transporters. Several ATP-binding cassette (ABC) transporters, such as P-glycoprotein (Pgp), multidrug resistance proteins 1–3 (e.g., ABCC2, MRP2), and breast cancer resistance protein (ABCG2, BCRP), significantly reduce the transplacental passage of drugs, therefore limiting their disposition into the fetal compartment [6]. After a drug has crossed the placental barrier, the total concentration of plasma proteins, as well as the protein-binding affinity for drugs, is low in the fetus in comparison to the mother. This results in a higher free fraction of the drugs in the fetus, which facilitates tissue distribution. On top of that, the permeability of the fetal blood-brain barrier is relatively high, and the immature central nervous system appears generally more sensitive to drug effects [9, 10].

Moreover, the hepatic mechanisms of drug elimination are not mature in the fetus (less activity and a smaller concentration of certain microsomal enzymes), and this results in a reduced rate of drug metabolism, as well as an increased drug accumulation in the fetal compartment. Drug metabolism in the fetal liver is more likely to be more active than the drug metabolism in the placenta [9]. In the late stages of

gestation, and approximately during the first 3 months of life, the metabolic capacity of the fetus/newborn is relatively low, exposing it to high quantities of almost any drug administered to the mother [11, 12]. The drug metabolites in the fetus are either products of the limited fetal metabolism, or compounds of maternal origin. Once these metabolites are present in the fetus, they cannot be easily transferred back to the maternal blood [10]. After delivery, the physiologic mechanisms of the newborn also undergo changes. After the first 3 months of life, the hepatic enzymes have developed, although the maturation rate seems to vary among subjects [12]. Lastly, for the majority of drugs, excretion is reduced as the neonate's glomerular filtration rate is proportionally lower in comparison to adults [9].

2.1.3 Pharmacokinetics of Anxiolytics in Pregnancy

Benzodiazepines cross the placenta and reach the fetus through diffusion, which is not constant across pregnancy. In late pregnancy, changes in the placental circulation, size, permeability, and lipid content lead to an increased diffusion in comparison to early pregnancy. In addition, some benzodiazepines have long half-lives, and long-term administration may lead to drug accumulation in the maternal and fetal compartments. Even after a single dose or until a steady state is achieved, the fetal levels of benzodiazepines may be even higher than maternal levels, due to the rapid maternal drug distribution. For instance, after an intravenous or oral single dose of diazepam, the fetomaternal ratio increases from 1.2 (i.v.) and 0.4 (oral) in early pregnancy, to 1.8 (i.v.) and 0.8 (oral) in late pregnancy [13].

Regarding diazepam, the fetus is able to metabolize it from the 13th week of gestation, although, in the early stages, the metabolic rates are particularly low for both the placenta and the fetus. As a result, diazepam and its metabolites accumulate in the fetus [14, 15]. Thus, after administration of high higher diazepam doses in late pregnancy, newborns can be affected, and high levels of the drug are detected in their circulation.

On the other hand, oxazepam has a relatively short half-life and lacks active metabolites. Pregnant women have a shorter oxazepam half-life and higher clearance. After oral oxazepam administration, the fetomaternal ratio is 0.6 and 1.1 in early and late pregnancy, respectively. During the late stages of gestation, fetal levels are higher than the maternal ones. This indicates that, during this period, there is increased diffusion of benzodiazepines through the placenta, high maternal volume drug distribution, and high maternal metabolic and elimination rates [14]. Regarding the neonate, oxazepam has three to four times longer half-life, in comparison to the mother, but after the first few days of life, oxazepam elimination in the infant is increased, probably due to more effective glucuronidation and renal excretion [13, 16].

Chlordiazepoxide was primarily used as a labor sedative, and it has been shown that after a single dose of chlordiazepoxide during labor, the fetomaternal drug ratio is near 1. Chlordiazepoxide's half-life in the newborn is 20% higher than normal, but no symptoms of sedation have been reported in neonates [13, 17].

Regarding lorazepam, moderate perinatal doses are considered safe for the mother and the newborn. Lorazepam diffuses rapidly across the placenta, and fetal concentrations are similar to maternal concentrations. The infant metabolism of lorazepam does not differ significantly from the mother's, it has no active metabolites, and plasma levels are reduced within 7 days [13, 17]. Similarly, it has been shown that the flunitrazepam fetomaternal dose is 0.22 after a single dose of oral flunitrazepam administered in late pregnancy. Drug concentrations in the cord, umbilical vein, and artery plasma are lower than those in maternal venous plasma, and amniotic fluid levels are negligible. However, the long-term use of flunitrazepam during pregnancy is associated with a high possibility of accumulation in the fetus due to the drug's long elimination half-life. Likewise, a single dose of oral nitrazepam during delivery or in early pregnancy results in a fetomaternal plasma concentration ratio between 0.4 and 0.9. Maternal plasma levels of nitrazepam do not differ between early and late pregnancy, but fetal plasma levels are higher in the late stages of gestation [13].

Finally, zopiclone and its metabolites pass through the placental barrier to a limited degree. One study showed that concentrations of total radioactivity and concentrations of the unchanged compound in fetal tissues were 3–4 times lower than those in the placenta. Amniotic fluid concentrations of total radioactivity were also low [16].

2.1.4 Pharmacokinetics of Antidepressants in Pregnancy

During pregnancy, the increased metabolism, as described above, reduces the levels of many antidepressants, such as sertraline, citalopram, fluoxetine, paroxetine, and venlafaxine, and thus their overall availability [2]. However, because some antidepressants have active metabolites (as other psychotropics as well), fetal exposure to an active metabolite may unpredictably increase due to the increased metabolism of the parent drug during pregnancy. Indeed, whereas sertraline, citalopram, and fluoxetine levels are reduced during pregnancy, a higher metabolite to parent drug ratio is found during late pregnancy [5]. Likewise, bupropion levels decrease during pregnancy, and the drug is undetectable in the fetus. However its active metabolite reaches significant levels in the pregnant mother and can be detected in the fetus, with potentially hazardous consequences [18, 19]. Paroxetine levels may also decrease, especially if the pregnant woman is an extensive or ultrarapid metabolizer. On the contrary, in pregnant women with intermediate and poor metabolizing genotypes, increased plasma levels can be observed, with potential consequences to the fetus [5]. Moreover, the administration of an antidepressant with short or long elimination half-life will determine whether it is more likely to cause fetal withdrawal symptoms or toxicity [20]. Another issue regards the transport proteins during pregnancy. Some antidepressants may further inhibit the already downregulated Pgp in pregnancy, and Pgp genetic polymorphisms may result in significant individual differences in drug exposure to the mother and the fetus [6, 21]. Fluoxetine, paroxetine, and sertraline are especially prone to Pgp-related effects. Regarding other classes of

antidepressants, clomipramine has an increased elimination half-life, and along with its active metabolite, they have a *F*/*P* ratio of 0.5–0.8 [73]. It is known that nonpregnant women have a higher exposure than men to venlafaxine and duloxetine [4, 5], but very few pharmacokinetic data exist on venlafaxine and duloxetine.

2.1.5 Pharmacokinetics of Antipsychotics in Pregnancy

Examining antipsychotic drug fetal exposure during pregnancy, a study indicated that olanzapine and haloperidol had the highest placental passage ratio (mean of 72.1% and 65.5%, respectively). Risperidone follows (mean = 49.2%), as well as quetiapine, with the latter having the lowest passage ratio of all antipsychotics (mean = 23.8%). Notably, quetiapine and risperidone are atypical antipsychotics found to share a good P-glycoprotein (Pgp) affinity, and as a result placental Pgp is able to reduce the placental passage of these drugs. On the other hand, olanzapine and clozapine are intermediate and poor substrates, respectively. Their low affinity for the Pgp efflux transporter results in an easier passage through the placental barrier, due to their lipid solubility, without being hindered by the Pgp efflux transport [22]. Moreover, quetiapine is metabolized primarily by CYP3A4, which is induced in pregnancy. This explains the rapid elimination and low plasma concentration of quetiapine in most pregnant women. In fact, a dose increase may be required during pregnancy, and a postpartum decrease would avoid toxic side effects, as quetiapine's bioavailability is much higher in the postpartum period than in gestation [23, 24].

2.1.6 Pharmacokinetics of Mood Stabilizers in Pregnancy

Most mood-stabilizing drugs (lithium, valproic acid, carbamazepine and lamotrigine) cross the placenta, a fact proven by either detectable levels in cord blood or by their teratogenic and fetotoxic effects in animals [25]. Even in the early stages of pregnancy, the lithium clearance increases by 50–100%, because of the increased renal function. As a result, serum lithium concentration decreases significantly. In the postpartum period, lithium clearance rapidly returns to baseline values, and along with the normalization of other pregnancy-related pharmacokinetic parameters, the dose adjustment of lithium becomes of significant importance [26, 27]. The relative lithium concentration in umbilical cord blood to maternal blood is 1.05, a ratio that remains constant for a wide range of lithium serum concentrations [28].

Regarding valproate, its absorption does not seem to change in pregnancy, but the total blood levels apparently decrease in pregnancy along with an increased volume of distribution. However, the unbound, active fraction (normally 10%) may not change. This happens because on one hand, there is increased clearance of the unbound valproate, due to increased renal clearance and lower protein-binding sites in pregnancy. On the other hand, this effect is compensated by increased binding in tissues and altered drug metabolism. The total effect of all these complex pharmacokinetic changes may be no significant difference in free valproate levels during

pregnancy. However, postpartum levels may increase rapidly, requiring dose adjustment. Moreover, valproate and its metabolites are found in higher concentrations in the fetus than maternal blood, as the neonate/maternal blood ratio has been estimated at 1.3–4.6 [26, 29, 30]. These increased valproate concentrations suggest that the fetus may function as a deep compartment for the drug's distribution, the drug is actively transported through the placenta, or valproate binds fetal serum proteins with higher affinity.

Lamotrigine binding to plasma proteins is only 55%, and this does not change in pregnant women [31]. Lamotrigine metabolism is significantly affected in pregnancy, albeit with significant variations among women. In pregnancy, metabolism and clearance of lamotrigine increase, resulting in lower plasma levels and a 40–300% higher dose-to-plasma concentration ratio. However the lower plasma concentrations are observed when lamotrigine is administered alone and not when co-administered with valproate [32, 33]. Plasma lamotrigine levels also present pulsatile variations within the day, possibly due to hormonal or other physiological changes in pregnant women, but this phenomenon has not yet been studied thoroughly. After delivery, lamotrigine clearance quickly reverts to its prepregnancy levels [31, 34]. Notably, lamotrigine is extensively transferred to the newborn, reaching levels similar or greater than the maternal ones [25, 32, 34]. After birth, the newborn clears the drug at a slow rate, because of immature glucuronidation and undeveloped renal excretion [34].

Carbamazepine, oxcarbazepine, and metabolites also decrease during pregnancy, but their concentration in cord blood equals maternal serum levels. The placenta metabolizes oxcarbazepine into its active metabolite (10-OH-CBZ), but it does not metabolize carbamazepine or 10-OH-CBZ. Moreover, carbamazepine's induction of CYP3A4, resulting in induction of its own metabolism, does not take place into the placenta, which lacks CYP3A4 activity. Finally, all substances readily cross the placenta and affect the fetus, with 10-OH-CBZ showing a slower transfer due to its lower liposolubility [31, 35].

2.1.7 Pharmacokinetics of Opioids in Pregnancy

Opioid pharmacokinetics depend heavily on the observed changes in the metabolism, induced by pregnancy, and importantly in the CYP2D6 and the Pgp enzymes, whose substrates include many opioids. Because of several genetic CYP2D6 polymorphisms, resulting in poor, intermediate, extensive, and ultrarapid metabolizers, opioid pharmacokinetics are difficult to predict in pregnancy. Generally, throughout gestation, CYP2D6 activity gradually increases in ultrarapid and extensive metabolizers and decreases in poor and intermediate metabolizers. Moreover, pregnancy increases the renal Pgp activity, which excretes morphine to the urine, and the placenta itself has been proven to express P-glycoprotein in mice [36]. In particular, fentanyl administration during pregnancy is not well-studied, and one case report found low fentanyl concentrations in the newborn at birth [37]. Women in methadone maintenance have lower plasma levels and lower half-life (19 h vs. 30 h)

possibly due to the enhanced CYP3A4 and CYP2B6 activity, the higher plasma volume, the larger tissue reservoir, and the metabolism in the fetus and the placenta. Moreover, methadone renal clearance and elimination are significantly increased during pregnancy. Those changes require the administration of larger and more frequent methadone doses in pregnant women [38–41].

2.2 Pharmacokinetics of Lactation

Many women require psychotropic medication during the postpartum and lactation periods. As a result, there is concern for the potential infant exposure through the breast milk. The pharmacokinetics of psychotropic drugs in lactation are examined in three distinct stages: (a) pharmacokinetics in the lactating mother, (b) drug excretion into the breast milk, and (c) pharmacokinetics in the newborn that receives the drug through breastfeeding [42]. Few studies have focused on the pharmacokinetics of psychotropics during lactation, and even fewer have employed high-quality methodology [42, 43]. Ethical issues, the process of taking frequent samples from mothers and infants, carrying out a long-term prospective study, and measuring concentrations are difficulties that have contributed to the lack of adequate studies. The results are often contradictory, and the conduction of a meta-analysis would be impossible due to the heterogeneity in the measuring methods [44]. As a result, the strong suspicion that most psychotropic drugs enter breast milk and the lack of substantial evidence on infant dose, kinetics, and safety have pushed clinicians towards a conservative attitude toward breastfeeding for women on psychotropic medication. Nonetheless, there is some methodology in place and some knowledge that should allow more informed decisions. Breast milk pumping at regular intervals within 24 h is a method that simulates normal feeding. Psychotropic drugs can be measured in the breast milk, with concentrations corresponding to an infant's daily ingested dose. If blood is drawn from the mother, preferably at the same time as milk pumping, the milk-to-plasma concentration ratio can be calculated. The *M*/*P* ratio for each drug varies, depending on dosage interval and time of sampling. The estimated drug exposure of the infant can be expressed as a percentage of the normal dose adjusted for weight and age (in mg/kg) or more frequently as a percentage of the maternal dose [45, 46]. An *M*/*P* ratio of less than 1 suggests negligible excretion to the milk, and a drug is generally considered safe if the relative infant dose is less than 10% of the maternal dose [47, 48]

2.2.1 Pharmacokinetics in the Lactating Mother

The effects of lactation on pharmacokinetics have not been studied and remain largely unknown. All the physiologic changes of pregnancy (e.g., increased plasma volume, decreased plasma proteins, increased renal function) revert to normal after delivery, but this return may be gradual, affecting drug concentrations in the postpartum period. For instance, while maternal caffeine clearance reverts to baseline

within days, phenytoin clearance takes months to reach its prepregnancy levels. Labor and delivery may also impact pharmacokinetics, as they result in physiologic stress, decreased plasma volume, and other changes [45].

2.2.2 Drug Excretion to the Breast Milk

A drug's concentration in breast milk varies and depends on its chemical properties (lipophilicity, molecular weight, degree of ionization), the characteristics of the milk (pH, protein and lipid content), as well as the maternal pharmacokinetics (dose, frequency, absorption, blood flow to the breast, and drug metabolism by the mammary tissue). Breast milk is not a reservoir where drugs accumulate but rather a compartment where drugs undergo bidirectional transfer, being in a continuous equilibrium with blood plasma. In order to calculate an infant's drug exposure and milk yield and intake, drug concentration and the presence of active metabolites must be measured. There are also differences in drug concentrations when the two breasts are compared, as previous feeding may affect milk yield and drug excretion [45]. The timing of the dose is also important, as the infant will be exposed to smaller drug quantities if feeding and medication times are arranged correctly. Immediate-release drugs, taken immediately after breastfeeding, will have lower concentrations in breast milk after a few hours [48]. Psychotropic drugs are lipophilic—as they need to cross the blood-brain barrier to reach their site of action—and can easily penetrate into breast milk via passive diffusion [49]. Highly lipid-soluble and unionized molecules diffuse more rapidly through the membrane, and this is shown by a measured milk-to-plasma concentration ratio approaching 1. A milk-to-plasma ratio of 1 or higher is generally considered significant exposure for the infant [10]. Breast milk has a higher lipid content than plasma, resulting in high concentrations of psychotropic drugs, most of which are lipid soluble. Colostrum, which is produced from day 1 to day 5 postpartum, has a mean lipid concentration of 29 g/L, and mature milk has a 42 g/L concentration. Hindmilk also has more fat than foremilk and thus contains larger quantities of psychotropic drugs. The main drug-binding proteins in breast milk are α-lactalbumin, casein, and lactoferrin. Colostrum has a total protein concentration of 23 g/L; mature milk (>30 days postpartum) has 9 g/L of protein, while blood plasma has more than 60 g/L. Hindmilk (at the end of a feeding) has a 50% higher protein content than foremilk. Concentrations of protein-bound drugs follow these fluctuations. The percentage of unbound drug in the milk remains stable regardless of its concentration and depends on the milk's pH [9, 42, 45]. Milk pH is usually lower than plasma pH. It varies from 6.35 to 7.65 and gradually decreases as the milk matures. Most psychotropic drugs are weak bases and thus diffuse readily down the pH gradient. Once in the breast milk, the low pH induces ionization, and ionized drugs become more water soluble and may be trapped in the breast milk [10, 45, 46, 48, 50]. Finally, ingredients such as lactose, serum albumin, calcium, phosphates, and various enzymes also affect drug concentrations in breast milk [51].

2.2.3 Pharmacokinetics of Nursing Infant

An infant's drug exposure depends not only on the dose ingested with breast milk, but also on its own pharmacokinetics, for which infant age is the determining factor [46]. The particulars of breastfeeding (suckling time on each breast, amount of milk ingested, and feeding intervals) also play an important role [42]. In studies assessing drug safety, a 100% oral bioavailability with no first-pass metabolism is usually assumed so as to examine the "worst-case scenario." However, gastrointestinal absorption of drugs has not been studied adequately in infants. It is believed that irregular motility and slow gastric emptying affect absorption rate. Stomach acidity is developed within the first day of life. For the next 8 days, pH returns to neutral and then descends to adult levels within 2 years. For all these reasons, the total amount that is eventually absorbed may be smaller, equal to, or larger than the equivalent amount in adults [44, 46].

Drug distribution also displays significant differences between infants and adults, because of differences in total body water, extracellular fluid, fat and muscle content, pH, and protein binding. The protein-bound fraction of drugs is lower in infants, owing to a different albumin structure, decreased albumin and globulin concentration in the first year of life, and increased bilirubin and free fatty acids, which bind to the available binding sites. Thus, drugs binding to albumin have a higher free, active fraction in infants [42, 44–46]. Newborns also have an immature blood-brain barrier, and CSF concentrations of lipid-soluble drugs can be 10–30 times higher than plasma concentrations. Fat quantity is also decreased, and lipid-soluble drugs have fewer storage sites, thus accumulating in the nervous system in higher concentrations [51].

Drug metabolism and excretion occur at a slower rate in neonates. Preterm infants have even slower metabolism and excretion rates and should not be exposed to psychotropic drugs through lactation [50]. Cytochrome P450 is an important enzyme for the metabolism of certain psychotropic drugs. The newborn has only one-half of the enzymatic activity of an adult, and this can have an effect on drug metabolism. Especially during the first 2 weeks of life, enzymatic activity in the liver is estimated at 20% of adult activity. Like all liver enzymes, CYP matures after birth, slowly reaching maximum activity [48]. The enzymes that take part in phase 1 reactions (oxidation, reduction, and hydrolysis) mature quickly and reach higher levels of capacity during years 0–3 than they do in adult life. Stable levels are not reached until puberty. Isozymes of CYP mature at different rates: CYP1A2, CYP2C19, and CYP2D6 have low capacity in infants, while CYP3A has higher capacity. Genetic polymorphisms leading to high or low enzyme activity in adults ("poor" vs. "extensive" metabolizers) have the same effects in infant age [46]. Moreover, unique metabolic products produced only in infants have also been documented, as is the case with chlorpromazine [42]. Phase 2 reactions (conjugation and glycine sulfate formation) are known to exhibit high interindividual variability because of genetic polymorphisms and reach adult capacity at 1.5–2 years of life. If glucuronidation is the only metabolic pathway available for a drug (e.g., oxazepam), infant concentrations will be significantly increased. As mentioned before,

each enzyme develops the ability to metabolize different substrates at different time points during maturation. For instance, glucuronyl transferase can metabolize bilirubin on day 3 but cannot fully metabolize chloramphenicol before day 10. Premature infants have even more pronounced enzyme immaturity [44, 46, 50, 51].

Despite having proportionally larger kidneys, neonates exhibit a glomerular filtration rate of 2–4 mL/min, i.e., only 30–40% of the adult GFR and 20–30% of the adult tubular secretion. Drugs are thus excreted more slowly and can easily accumulate and reach toxic levels. Preterm infants' kidneys are even less developed. The GFR and tubular secretion mature to adult levels within 2–5 months and 5–9 months of life, respectively [42, 51]. However, renal excretion is not the primary route of elimination for most psychotropic drugs (with the exception of lithium) [46]. Moreover, breastfeeding is usually fully initiated after the second day of life (when the GFR has already tripled), decreasing the danger of toxic drug accumulation [44]. In general, drug exposure through breast milk is lower (and thus safer) than exposure through transplacental transfer, unless the infant is premature or has a metabolic defect [52].

2.2.4 Pharmacokinetics of Anxiolytics and Hypnotics During Lactation

Most anxiolytics are passively diffused into breast milk due to their lipophilic, unionized, and highly protein-bound profile. Clinicians tend to prefer short-acting benzodiazepines and avoid repeated administration that would lead to steady-state pharmacokinetics and increased infant exposure [53]. For example, oxazepam has a short half-life, does not ungergo liver demethylation or hydroxylation, and has no active metabolites. Whereas conjugation occurs more slowly in neonates, oxazepam conjugation is sufficiently effective within 1 week of life [46]. Milk-to-plasma (*M*/*P*) ratio varied from 0.1 to 0.3, and the infant exposure was found to be less than 1/1000 of the maternal dose [54, 55]. Lorazepam's *M*/*P* ratio varies from 0.15 to 0.26, and its milk concentration is negligible [54]. B-glucuronidase activity reduces lorazepam ingested by the infant to 6.1% of the weight-adjusted maternal daily dose [17], and only mild sedation of the infant has been reported in a study of 51 lactating women [55]. Midazolam's *M*/*P* ratios are 0.09–0.16, and the exposure of the infant is 0.1% of the adjusted maternal single dose [17, 54]. Prazepam and temazepam *M*/*P* ratios ranged from 0.10 to 0.14, and they are not detectable in the infants' serum during lactation [10, 54]. On the contrary, lormetazepam is detected in both breast milk and plasma of nursing infants, and milk concentrations increase with each day of administration [46]. Alprazolam's milk-to-maternal plasma ratio was approximately 0.36, and the infant exposure was 3% of the maternal dose [54]. Clorazepate and its metabolite nordiazepam are transferred into milk during lactation. The drug's very short half-life indicates that the detected product is most probably nordiazepam. Total clorazepate concentration found in the milk accounted for 15–30% of maternal plasma levels, and infant plasma levels accounted for 50% of the milk drug concentration [56]. Diazepam and its metabolites are found in the breast milk, and infants exposed

to diazepam may have longer lasting neonatal jaundice because of decreased bilirubin conjugation [9]. Even after a single postpartum higher dose administered to the mother, diazepam and its active metabolites can be detected in the breast milk and maternal and infant plasma for 6 days, following an accumulation pattern. The relative dose (diazepam and demethyl-diazepam) ranges from 2.6% to 13.4% of the mother's dose and 4–5% of the pediatric dose. Plasma concentrations in newborns range from 35% (diazepam) to 71% (demethyl-diazepam) of the maternal concentration after 4 days of life to 12% (diazepam) and 6% (demethyl-diazepam) [46]. Nitrazepam also accumulates in the maternal plasma and breast milk, and repeated administration or higher doses should be of concern [13].

Interestingly, zopiclone, zolpidem, and zaleplon have very short half-lives, as well as fast elimination, making them less likely to accumulate in infant tissues. Their *M*/*P* ratio varies between 0.13 (zolpidem) and 0.6 (zopiclone), and the estimated infant exposure through breastfeeding should be less than 5% [16, 45, 50, 55, 57].

2.2.5 Pharmacokinetics of Antidepressants During Lactation

Regarding all selective serotonin reuptake inhibitors (SSRIs), the lactating infant is exposed to less than 10% when the relative infant dose is expressed as a percentage of the maternal dose [58]. Such exposure is considered to be lower than the in utero exposure of the fetus. As a result, blood measurements of SSRI in lactating infants often show concentrations that are negligible or below the detection limit of the employed method. However, significant variations are reported in the literature. In fact, the relative infant dose ranges are: 5-7% for citalopram and escitalopram, 3-6% for fluoxetine and norfluoxetine, 0-1% for fluvoxamine, 0-1% for paroxetine and 0-3% for sertraline. When researchers found detectable levels of an antidepressant in lactating infants, the calculated *M*/*P* concentration ratio was also low. For example, the fluoxetine ratio was 0.3, and the ratio of its metabolite norfluoxetine was 0.2 [51, 59–61].

Regarding the serotonin-norepinephrine reuptake inhibitors, duloxetine displayed a 0–1% relative infant dose, and venlafaxine showed some accumulation in the milk with a relative infant dose of 3.2% [50]. Current evidence taken together suggests that fluoxetine and mostly citalopram (and escitalopram) may result in higher risk for the lactating infant, whereas sertraline, paroxetine, and fluvoxamine probably carry the lowest risk [51, 53]. An additional benefit of sertraline is that it has a relative short half-life, and thus it can be administered once daily in a lactating mother, who can time the breastfeeding (or pumping) accordingly. Regarding the tricyclic antidepressants, most of them are detected in breast milk as they are bases and can be trapped in it. Tricyclics have large volumes of distribution and variable serum levels in lactating infants, ranging from nondetectable to notable. Indeed, the relative infant exposure for clomipramine was calculated at 3–4%, whereas for amitriptyline and nortriptyline, it was approximately 2% [45, 51]. Nowadays the use of tricyclic antidepressants is limited in most countries, but if they need to be prescribed, amitriptyline and imipramine are recommended [50].

2.2.6 Pharmacokinetics of Antipsychotics During Lactation

Milk/plasma ratios for first- and second-generation antipsychotics are mostly below 1, and with a few notable exceptions, infant exposure is generally modest. Thus, accumulation of antipsychotics in the newborns is unlikely, as infant plasma and urine drug levels are low [22]. Breast milk levels of zuclopenthixol, perphenazine, trifluoperazine, haloperidol, and chlorpromazine were 1–3% of the maternal daily dose [48, 62]. The milk-to-plasma ratio for haloperidol was 0.67, for chlorpromazine between 0.5 and 1, and for perphenazine closer to 1. However, mothers on combined haloperidol and chlorpromazine treatment had increased blood and milk levels of both drugs [45, 46, 50, 63].

Regarding second-generation antipsychotic agents, infant estimated exposure to olanzapine, risperidone, and quetiapine during lactation is not considered significant, and these drugs have very low concentration in the plasma of the lactating newborn. Olanzapine levels in infant plasma are undetectable, and infant exposure has been estimated to 1.8% of the maternal dosage [50]. Risperidone and its active metabolite 9-hydroxyrisperidone (paliperidone) have *M*/*P* ratios of 0.42 and 0.24, respectively, and the estimated infant exposure is 4.3% of weight-adjusted maternal daily dosage [62]. Infant exposure to quetiapine is probably modest, as doses of 75 mg or less are generally not detected in the breast milk, but in one case, a dose of 400 mg showed significantly higher milk drug concentrations [64]. On the other hand, clozapine is known to accumulate in breast milk and fetal serum and is contraindicated in breastfeeding women [50]. In fact, measured clozapine levels in the lactating infant were 2.8–4.3 times higher than in the maternal plasma [22, 62]. Finally, very few and inconclusive data exist on amisulpride, aripiprazole, ziprasidone, asenapine, and sertindole [22, 48]. A note of concern is that, following an evaluation by Hummels et al., very few studies regarding antipsychotics and lactation correctly reported the *M*/*P* ratio, the absolute infant dose (AID), and the relative infant dose (RID), thus raising some concerns about the quality of the evidence so far [65].

2.2.7 Pharmacokinetics of Mood Stabilizers During Lactation

The free, unbound fraction of mood-stabilizing drugs can be excreted into breast milk, where no protein binding occurs [30]. Importantly, if a lactating mother is treated with lithium, the drug is detected in both breast milk and infant serum. Milk levels highly correlate with plasma levels in low lithium concentrations but can reach 1.5 times the plasma level, in higher concentrations. Consequently, mean breast milk levels are approximately 40% of the maternal serum levels, but levels higher than 50% have also been observed. Accordingly, infant plasma concentrations are between 10% and 50% of maternal levels and 80% of the weight-adjusted dose. In addition, infants also lack the ability to excrete large lithium quantities, and infection or dehydration can exacerbate this inability, thereby increasing lithium concentrations [25, 26, 46, 60].

On the contrary to lithium, valproate levels in breast milk are low, corresponding to 5% or less of maternal serum concentrations, as shown by various studies [34, 66, 67]. The dose found in infants corresponds to less than 6% of the initial pediatric dose for epilepsy [46]. Despite low levels of valproate, there is some risk involved, because of potential fetal hepatotoxicity [9]. Regarding carbamazepine, the milk-to-plasma ratios are found between 0.4 and 1.8, and infant blood levels range from 6% to 65% of maternal blood concentration [34, 44]. However, carbamazepine is considered to have a more favorable pharmacokinetic profile than lithium, as the final exposure of the lactating infant corresponds to only a fraction of the lowest therapeutic dose after weight adjustment [26, 46]. Finally, lamotrigine is also excreted, and the breast milk/maternal plasma ratio may vary considerably between 40% and 60%, and even as high as 150%, as shown by several studies [25, 28, 32, 34]. Lactating infants eliminate lamotrigine slower and therefore are prone to display enhanced lamotrigine levels. Moreover, it should be highlighted that lamotrigine serum levels in the mother undergo a rapid increase immediately after delivery, thus loading the breast milk with high lamotrigine concentrations [28].

2.2.8 Opioid Pharmacokinetics During Lactation

It is long known that codeine and morphine display low concentrations in breast milk. Codeine is rapidly eliminated, and it is undetectable in the breast milk 14 hours after administration. However, its active metabolite, morphine, remains in breast milk for more than 36 hours, but codeine and morphine serum levels in the infant remain low. Administration of morphine per se results in a 4% of the maternal weight-adjusted dose being finally ingested by the infant. Low infant morphine levels are due to extensive first-pass metabolism, but infants are more sensitive to lower morphine doses than adults [45]. Despite the apparent safety of codeine and morphine, caution should be exerted as a rapid/ultrarapid metabolizing mother can transform increased amounts of codeine to morphine, thus overdosing the lactating infant which has low capacity of morphine glucuronidation [36]. Following transdermal fentanyl administration to the lactating mother, fentanyl and its metabolite, norfentanyl, are undetectable in the infant's blood. Fentanyl excretion is low in milk, and the exposure of the lactating infant corresponds to 10% of the one-time oral dose recommended for anesthesia in children. Such low doses are unlikely to exert any effects [37]. Tramadol is frequently used for labor analgesia, and its kinetics in the newborn and breast milk are relatively well-studied. The relative infant dose of tramadol and its metabolite, *O*-desmethyltramadol combined, is calculated to approximately 3% [68]. Tramadol metabolism in the neonate is adequate and becomes substantial over the first year of life, but in return, accumulation of its metabolite can take place due to its limited excretion [69]. Regarding methadone, its breast milk levels are modest. Ingested methadone through breastfeeding is calculated to be 0.1–0.3 mg daily, and the weight-adjusted dose for the infant is low, approximately 2.8% of the maternal dose. However, there have been scarce reports of a neonatal abstinence syndrome after breast milk feeding was discontinued [70, 71].

2.3 Conclusions

Pregnancy results in a myriad of physiological changes, and unavoidably this leads to significant changes in the pharmacokinetics of nearly all psychotropics. Unfortunately, whether these changes are clinically important or not has not been clarified yet [2]. Moreover, it becomes immensely more difficult to clarify the final net effect of those changes, as many alterations have effects that cancel each other. Notably, although the placenta barrier normally protects the fetus, this does not apply to psychotropic medications, which are designed to penetrate human barriers, such as the blood-brain barrier and thus also the placenta. As a result, there is no "safe" drug in pregnancy, and pharmacokinetic data should merely be interpreted as aids in the "risk-to-benefit" decision-making processes made by clinicians. Randomized trials and well-designed pharmacokinetic studies in pregnant and lactating women would significantly improve our knowledge. Both kinds of studies are unlikely to occur, even for psychotropic medications routinely or widely used, as the pharmaceutical industry lacks the financial incentive to study those special populations and the regulatory framework is, righteously, very strict. Even if all these obstacles were overcome, the recruitment for such studies would be very problematic [72].

Based on current limited data, some prescribing strategies based on pharmacokinetics can be concluded: dose reduction during pregnancy is not always as attractive a strategy as it initially sounds, except for very specific cases. Pregnancy itself results in a reduced bioavailability of many medications, and for many psychotropics, there is not a clear or linear dose-response curve [74]. As a result, clinicians should carefully assess the risk of disease exacerbation or recurrence and even consider a dose increase, if required. From a pharmacokinetic point of view, in order to minimize the exposure of the fetus to a psychotropic medication, higher protein binding, smaller distribution volume, shorter half-life, and ideally good affinity with efflux transporters are characteristics that would make one psychotropic medication more suitable than others for pregnant women. In any case, combinations of drugs should be avoided, especially those involving extensive P450 metabolism, as the cytochrome is heavily modulated by pregnancy and interactions cannot be easily predicted.

Regarding breastfeeding, traditionally women on psychotropic medications were discouraged from it, a recommendation mostly based on principle rather than firm evidence. Alternatively, psychotropic medications were discontinued if breastfeeding was chosen, but this practice also ignores the individual characteristics and pharmacokinetic profile of each psychotropic medication. It is considered that infant drug concentration of 10% or less of the maternal drug therapeutic dose is a safe infant exposure, and for several psychotropic medications, there is evidence (though still not unequivocally firm) that they have nearly undetectable levels in the lactating infant [74]. A word of caution for those drugs that display low to moderate levels in the systemic circulation of a lactating infant is that brain concentrations can be significantly higher, or more impactful, due to the immature blood-brain barrier and brain tissue [60]. Specific strategies can be implemented to further reduce the exposure of the infant, i.e., selection of psychotropics with shorter half-life,

administration at the lowest effective dose, and breastfeeding and/or pumping milk (for later feeding), just before the scheduled time to take the medication [10, 51]. Breastfeeding mothers should be well-informed and educated, in order to observe for potential adverse effects [11, 53]. Infant age should also be taken into consideration, as the potential risks progressively diminish with the maturation of the infant's hepatic metabolism and renal clearance. In any case, premature infants should not be exposed to psychotropics [60].

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3 Safety Parameters and Risk Categories Used for Psychotropic Drugs in Pregnancy and Lactation

Yusuf Cem Kaplan and Hilal Erol-Coskun

3.1 Introduction

The perinatal period is associated with an increased risk of psychiatric disorders which may necessitate maternal pharmacotherapy. In this chapter, we aim to provide the reader with the basics of safety assessment regarding medication use during pregnancy and breastfeeding.

3.2 Pregnancy Risk Categories

Thalidomide disaster of the 1960s caused a drastic change in our understanding of risks regarding medication use during pregnancy. One of the important consequences of this incident, apart from those regarding the regulations regarding preclinical trials, was the emergence of a need to develop a categorization for the medications regarding the risks that are posed on a fetus, and this need led to the introduction of the different pregnancy risk categories in different countries.

The first risk category regarding medication use in pregnancy was developed and introduced in Sweden in 1978, named as the Swedish Catalogue of Approved Drugs (FASS), and four risk categories (A, B, C, D) have been proposed [1]. Category A denotes the safest drugs, and the possible risk of the medication is expected to increase from A to D. Category B comprises three subgroups (B1, B2, B3).

The following year (1979), the US Food and Drug Administration (FDA) introduced a pregnancy risk category system which was composed of five subgroups,

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Table 3.1 Short summary of pregnancy warning classification systems in Sweden, the United States, and Australia (From Källén [1] with permission)

Category
Sweden
(A) No known risk
(B) Human data insufficient
(B1) No fetal effects in animal data
(B2) Incomplete animal data
(B3) Fetal effects in animal data
(C) Pharmacological effects on fetus
(D) Causes or is suspected of causing fetal damage in humans
The United States
(A) Controlled studies show no risk
(B) No evidence of human risk (controlled studies show no risk or animal studies indicate no risk)
(C) Risk cannot be ruled out
(D) Positive evidence of risk but potential benefit may outweigh potential risk
(X) Contraindicated in pregnancy
Australia
(A–D) As in Sweden
(X) Should not be used in pregnancy

A–D, like the FASS, and an additional subgroup, X [2]. The Australian Drug Evaluation Committee (ADEC) classification was developed in 1989. ADEC can be regarded as a combination of both previous categories since it comprises subcategories B1, B2, and B3 and X [2]. Table 3.1 presents a short summary of these three systems. Important differences regarding the classification of the similar medications between these three systems were previously reported [2].

3.3 Criticisms Regarding the FDA Pregnancy Risk Categories

The primary aim of the FDA pregnancy risk categorization system was to provide an evidence-based risk assessment and therefore help the physician while counseling the women who are planning a pregnancy. It was not designed, however, as generally misunderstood by the health providers, for use to assess an exposure which happened during an inadvertent pregnancy. At the time the risk categories were designed, pregnant women were considered as young, healthy individuals who are free of diseases. However, this understanding has been changed since the last two decades witnessed an increasing rate of pregnancy in women aged 35 and older [3], which consequently led to an increase in the number of pregnant women who is entering pregnancy with a preexisting chronic disease that necessitates pharmacotherapy. For instance, about 40% of women in the reproductive age (19–45) are reported to be diagnosed with a chronic disease in the United States [4], and one in five pregnant women was reported to have at least one chronic disease in Germany [5].

Toward the end of the 1990s, the FDA recognized that the 1979 categorization system had important limitations and shortcomings which may misguide the clinical practice. A public hearing resulted in the following implications [6]:

1. Categories are inadequate in conveying the risk because of the oversimplified narrative.
2. Categories indicate that the teratogenic potencies of drugs in the same category are similar, which is a false perception.
3. Categories do not differentiate between the possible severity and incidence of the fetal adverse effects. They also do not distinguish between the time, dose, route, duration, and frequency of the exposure.
4. Categories focus on the drug use in planned pregnancies. They are insufficient in identifying risks for the exposures during an inadvertent pregnancy.
5. Categories do not distinguish and are insufficient to make a meaningful interpretation between animal and human data.

Following extensive reviews and thorough discussions with key stakeholders, the FDA decided to remove the pregnancy letter categories A, B, C, D, and X from the product labeling and replace it with the Pregnancy and Lactation Labeling Rule (PLLR) which is the narrative summary of the risk associated with the use of a medication during pregnancy and lactation. Three sections are designed to be included in the new pregnancy label: (1) fetal risk summary, (2) clinical considerations, and (3) data [7]. Each pregnancy label will begin with the contact information regarding the relevant pregnancy exposure registry, when available, a standard statement about the baseline risk of major congenital malformations and other adverse pregnancy outcomes that exist for all pregnancies regardless of medication exposure [6]. The fetal risk summary section will include a conclusion sentence describing the likelihood that the medication increases risk to the fetus. The possible fetal adverse effects of the medication such as structural malformations, fetal and infant death, physiological dysfunctions, and fetal growth abnormalities and their incidence, seriousness, reversibility, and correctability will be covered. The possible fetal risks will be also framed with regard to the dose, duration, and time window of the medication exposure [7]. The clinical consideration section will include information regarding the inadvertent exposure such as dose, critical time window for the possible risks, and the possible risks of underlying maternal clinical condition, if present. Neonatal concerns, and their severity and reversibility, associated with the use of medication will also be addressed. The possible effects of the medication on the duration labor and birth will also be included. Data section is planned to include a discussion of the available human and animal data. Animal data will be reviewed with regard to the species, dose ranges, human dose equivalents, and possible mechanism of action [6].

This rule took effect on 30 June 2015 and requires the medications and biological products approved after 30 June 2001 to revise the information found in the Pregnancy and Nursing Mothers subsections of product labeling [8].

3.4 Assessing the Possible Teratogenic Risk of Medications

3.4.1 Variables Related with the Administration of the Medication

3.4.1.1 Time of Administration

The time after conception to implantation (8–10 days) is considered as the "all-or-none" period which implies the exposure to any harmful agent of the embryo would either yield to the spontaneous abortion or intact survival. The embryonic period, in which the organogenesis takes place, starts after the implantation and lasts from 54 to 60 days after conception. This period where a set of complex cellular events take place, such as cellular migration and differentiation, is the most sensitive period of embryo to teratogenic insults resulting in structural malformations. The fetal period just starts after the organogenesis and continues to term. Growth and functional maturation of organs occur in this phase, and teratogenic exposure during this period usually ends up with the disruption in function or size of the organs rather than structural anomalies.

For most drugs, the main concern is the first trimester of pregnancy [9]; however, there may be exceptions. For instance, exposure to selective serotonin reuptake inhibitors (SSRIs) in late pregnancy was shown to be significantly associated with persistent pulmonary hypertension of the newborn, whereas a significant association with early pregnancy exposure was not apparent [10].

3.4.1.2 Dose of Medication

Valproic acid (VPA) constitutes an important example of dose-related teratogenicity. Studies report different dose categories in which the rates of structural malformations with VPA monotherapy are significantly increased; the largest increased risk is demonstrated with doses greater than 1000 mg per day [11, 12]. Tomson et al. reported the malformation rates regarding VPA monotherapy in pregnancy as 5.6%, 10.4%, and 24.2% with doses <700 mg/day, ≥700 to <1500 mg/day, and ≥1500 mg/day, respectively [13]. Regarding the neurodevelopmental abnormalities, a VPA dose greater 900 mg/day and 1000 mg/day is associated with a decreased total development score and IQ, respectively [14, 15].

3.4.1.3 Route of Administration

The route of administration is one of the major determinants of drug bioavailability, which is the ability of a drug to reach the systemic circulation and therefore the fetus. Retinoids are potent and well-established teratogens which constitute a good example for this issue. Systemic retinoid exposure has been demonstrated to increase the rates or major malformations up to 35% [16]. This high figure, which is only comparable to that of thalidomide, and some case reports with major malformations [17, 18] in the 1990s led to an increased teratogenic risk perception regarding topical retinoids. However, cohort studies [19–22] and a recent meta-analysis [23] demonstrated that inadvertent exposure to topical retinoids does not seem to increase the rate of major malformations which is in line with in vivo and in vitro

pharmacokinetic data suggesting that their dermal absorption is minimal and unlikely to result in fetal harm [24, 25]. However, a rare association suggested by the case reports still cannot be excluded and contraindicates their use during pregnancy.

3.4.1.4 Monotherapy vs. Polytherapy

Psychotropic drug polytherapy in pregnant women is a common practice [26]. However, data regarding the teratogenicity risk of polytherapy vs. monotherapy with psychotropic drugs are very limited; however, a few studies are worth mentioning. Tomson et al. reported that VPA is a primary determinant of the risk of major malformations regarding the combination therapy in pregnant women using antiepileptic drugs [13]. This finding confirmed the results of the previous studies which suggested that it was VPA and not the number of antiepileptic drugs in the combinations that was associated with the increased risk for major malformations [27, 28]. However, a recent study questioned this finding and suggested that topiramate, when used in polytherapy, is also associated with the increased risk of major malformations [29]. Second-generation antipsychotic monotherapy appears to pose less risk to the fetus when compared with polytherapy [26]. Nevertheless, this area remains to be further investigated.

3.4.2 Evaluating the Data

As previously mentioned, lack of available data regarding a particular drug's effects during pregnancy is one of the biggest challenges we face in the clinical setting. Because ethical concerns limit the availability of pregnant women for randomized controlled trials, data regarding the effects of a drug on fetus is not usually available at the time of its launch. It has been shown that 92.1% of the drugs which have been approved by FDA between years 1980 and 2000 and 97.7% of the drugs that have been approved between 2000 and 2010 lack adequate data at the time of their approval [30, 31]. It takes at least 6.0 ± 4.1 years to determine the teratogenic effect of a drug after its approval, while ruling out even takes much longer (9.1 ± 4.5 years) [31]. Knowing how to interpret animal and human data therefore becomes more critical.

3.4.2.1 Experimental Studies

Animal Studies

Although there are difficulties in extrapolating the results to humans, animal studies can provide important information regarding the teratogenic effects of drugs. However, their protocols should be well-planned, and results need to be reported and interpreted carefully in order to rule out any bias [32]. Detected malformations should be interpreted regarding the type and rate, since some malformations are common in some species. Variations, of which definition depends on different factors such as animal species, strain, supplier, and laboratory environment, should not

be reported and/or interpreted as major malformations. It should be also kept in mind that excessive maternal toxicity induced by the drug may lead to nonspecific developmental toxicity in the offspring [33].

3.4.2.2 Human Studies

Case Reports

Case reports are very useful tools in the field of teratology if used properly. Observation of a repetitive "rare defect" appearing after a "rare environmental exposure" [34] by the "astute clinicians" [35] has been a very effective way to detect teratogens. The identification of warfarin [36, 37], diethylstilbestrol [38], isotretinoin [39], fluconazole (only with high dose and prolonged use for systemic infections) [40, 41], and mycophenolate mofetil [42, 43] as human teratogens was originally based on case reports. However, case reports cannot provide any estimates regarding the absolute risk since they lack a denominator. Because it is quite common to report and publish the positive findings [44], case reports trying to associate drug exposure in pregnancy with relatively common major malformations, of which background risk is 3% in the general population regardless of any exposure, exist in the literature. The clinician should be careful in interpreting those findings and should only consider the ones reporting a unique and repeating pattern of malformations with a particularly rare exposure during pregnancy as a signal.

Epidemiologic Studies

The ethical barriers that exist for enrolling the pregnant women in randomized controlled trials make the observational cohort and case-control studies the primary sources of information for drug use during pregnancy. Both studies are mutually complementary in assessing the teratogenic risk of drugs.

The development of teratology information services (TISes), which counsel hundreds of pregnant women every year about drug use in pregnancy, and their networks such as MotherToBaby (formerly OTIS, Organisation of Teratology Information Services) [45] and European Network of Teratology Information Services (ENTIS) [46] contributed significantly to the field of teratology by enabling the implementation of multicentral prospective cohort studies. Prospective cohort studies undertaken by TISes have important strengths such as assigning the subjects before the outcome is known, identifying the precise exposure time and minimizing the risk of recall bias by prospectively collected data, and being able to match the subjects in the exposed and control groups with regard to potential confounders mentioned below [47, 48].

Recent developments in the information technology have also enabled national medical databases and birth registries as sources of data for conducting prospective cohort studies. Medicaid and private insurance claims databases in the United States, Saskatchewan Health Services Database in Canada, the General Practice Research Database in the United Kingdom, and Population Medical Databases in Nordic countries are important examples which enable relatively quick and inexpensive analysis of a data from a large population that is prospectively collected for routine purposes [49].

Case-control studies are designed to assess whether a specific type of exposure is associated with a specific outcome by evaluating both subjects with and those without the specific outcome. A major strength of these studies is their increased statistical power which is usually adequate to detect moderate increases in the rate of a specific malformation [50].

Meta-Analysis

Meta-analysis emerged as a powerful tool of epidemiology enabling the pooling of results from individual, yet comparable, studies [51]. This method is useful in assessing the possible teratogenic effects of drugs, by combining the data from observational studies, with an increased sample size and power. It may also offer subgroup analyses, such as organ-specific malformations, which are reported but not evaluated in individual studies.

3.4.2.3 Methodological Issues

Sample Size, Characteristics, and Follow-Up

The background rate for major congenital malformations is 3%. Very few teratogens (thalidomide, isotretinoin, valproic acid) increase this rate by a factor of more than 2, while most only increase a specific malformation rate. At least 220 exposed and control (unexposed) pregnancies will be required to show that the major congenital malformation risk is increased by a factor of 2.5, with a power of 80%. Prospective cohort studies, which are usually conducted by TISes, include a relatively small number of patients (<300). Although this number makes it difficult to detect a specific malformation rate, it is adequate to rule out the particular drug being a major teratogen. Another issue with these studies is that the pregnant women who call TISes voluntarily may not be the representative of the general population. Follow-up period of the infants is usually 1 year and limits the inclusion of the malformations which are identified later. Loss to follow-up of the pregnant patients due to technical reasons may also be a concern in some of these studies [52].

Recall Bias

Recall of drug use is a potential limitation of case-control studies due to the reason that mothers with malformed children may be better at remembering their drug use and course of pregnancies [50]. Selecting the children with different malformations in the control group is suggested to overcome this problem.

Confounders

Maternal age, parity, gestational week, previous miscarriages or birth of malformed infants, folic acid use, body mass index, maternal smoking, and alcohol or illicit drug use are important confounders in studies evaluating the association of structural malformations with drugs used in pregnancy [48]. Maternal and paternal IQ, socioeconomic status, and level of education are important for the studies which assess long-term neurodevelopmental outcomes in children. A recent study

suggested that severity of maternal depression, and not selective reuptake inhibitor antidepressants, was a significant predictor of a decreased behavioral score in infants aged 3–6 years [53].

Confounding by Indication

The risk of major and/or organ-specific congenital malformations has been demonstrated to increase in some chronic diseases regardless of drug use. For instance, diabetes and chronic hypertension in the mother has been associated with an increased rate of congenital malformations [54, 55]. Studies evaluating the possible teratogenic medications should consider and control, if possible, the effect of underlying diseases. Including an untreated disease group may be beneficial; however, the severity of the disease in such a group may also be lower since treatment is not required [56].

Meta-Analysis

Although considered as the evidence of highest quality, meta-analysis may include different forms of bias and limitations [51]. Search should include different medical databases and languages, while validated methods of quality assessment for the included studies should be chosen. In the context of observational studies, a rigorous systematic review of the included studies should be conducted, and results of the meta-analysis should be discussed with regard to possible confounders and limitations. It is now generally accepted that studies reporting positive findings are more likely to get published than studies reporting negative ones, which is called publication bias or bias against the null hypothesis and discussed elsewhere [44, 57], and may lead to erroneous interpretations regarding drug safety.

3.4.2.4 Important Points to Consider for Medication Use During Pregnancy

The background frequency of major congenital malformations is approximately 3%. Unfortunately, no consensus is available in scientific literature regarding the safety of a drug during pregnancy in terms of the exposed number of pregnancies without a detectable teratogenic signal. As Larsen et al. pointed out in their recent review, 200 first trimester exposures without any signs of increase in risk of malformations (80% power, 5% level of significance) would mean that the real risk is not more than three times higher than the background risk [58]. If the exposure number is increased to 700, the real risk factor would decrease to 2. In order to provide a real risk factor of 1.5, the number of exposed pregnancies without any detectable increase in risk would be 2000. However these numbers of exposures are not available for most of the drugs on the market. Further complicating the issue is that those estimates are identified for the general risk, and specific rare malformations, neonatal complications, and possible long-term effects are not considered in the computations above. Nevertheless, the European Medicines Agency considers 1000 prospective exposed pregnancies with known outcome in the first trimester without any detectable signal as strong evidence suggesting that the malformation risk is

unlikely [59]. If this data volume cannot be reached, then the risk assessment should be made according to the available amount of data. The clinician should always weigh the possible fetal risks of the medication against the consequences of untreated maternal psychiatric illness. A discussion regarding those issues, as well as the medical and personal priorities, should be held between the physician and pregnant patient before deciding to start, continue, or quit the pharmacotherapy.

3.5 Lactation

3.5.1 Factors Influencing the Passage of the Medication into the Breastmilk and Infant Exposure

3.5.1.1 Maternal Plasma Concentration and Plasma Protein Binding

Because passive diffusion is the primary pathway of medications to enter the breast milk, the maternal plasma concentration of the medication usually shows good correlation with the concentration of the medication in the breast milk depending on the other pharmacokinetic variables such as the plasma protein binding. A high volume of the distribution and plasma protein binding leads to a lower maternal plasma concentration and unbound (free) medication levels which results in lower breast milk concentrations. For instance, sertraline has a relatively high volume of distribution and plasma protein binding which leads to a lower maternal plasma and breast milk concentration [60]. On the other hand, lamotrigine's lower volume of distribution and plasma protein binding capacity leads to higher breast milk levels [60].

3.5.1.2 Size of the Molecule

Most medications, and so do the psychotropic drugs, are small enough to enter the breast milk. Exceptions are the larger molecules such as heparin.

3.5.1.3 Degree of Ionization

Medications should be nonionized in order to cross the membranes and enter the milk. Of importance, breast milk is relatively more acidic (pH 7.2) compared to the maternal plasma (pH 7.4) [61]. Weak bases such as codeine and amphetamines become ionized at this pH and may accumulate in the milk [61, 62].

3.5.1.4 Lipid Solubility

Mature milk, which has a relatively stable composition and produced by 2–3 weeks after birth, is composed of ions, proteins, and lipids. Some lipid-soluble drugs, such as citalopram, may become dissolved in the lipid droplets and be co-secreted which may lead to a higher concentration in a milk with high fat content (hindmilk) compared to the milk with low fat content (foremilk) [63]. However, the practical implications of this issue are unclear and unlikely to influence the choice of pharmacotherapy [61].

3.5.1.5 Pharmacogenomics

Pharmacogenomics of the mother and the infant may affect the exposure of the infant to the drugs in breast milk. This is particularly highlighted for opioids [64]. As one study reported, the adverse outcomes in the breastfeeding mother-infant pairs are significantly associated with the maternal risk genotypes in CYP2D6 and ABCB1 [65]. However, this domain should be further explored.

3.5.1.6 Oral Bioavailability

A drug with low bioavailability in adults is usually expected to behave similarly in neonates. For instance, drugs with large molecules, protein or peptide drugs (unstable in the gut), exhibit limited transfer to the milk and therefore suggest limited bioavailability of the orally ingested drug in the infant through the breast milk [63].

3.5.1.7 The Age of the Infant

The first 3 days of postpartum is the period in which many drugs and immunoglobulin, lymphocyte, leukocyte, macrophage, and maternal proteins are able to pass to the colostrum due to alveolar intercellular gaps. These gaps are closed after a week, and passage of most drugs and molecules is reduced. Although colostrum is able to contain higher drug concentrations than the mature milk, the amount of colostrum produced in the early postpartum period is expected to be low (30–100 mL/day). Clinicians should be more careful at this stage, because of the possibility of the high drug concentration in the milk and premature or unstable newborns have insufficient capacity to metabolize medications. The amount of milk taken by babies over 1 year of age is usually reduced, and consequently the drug intake will be less [66]. In a review investigating the adverse drug reactions seen in the breastfed infants whose mothers are using medications, 63% of the cases were observed in the first month (newborn), and 16% were in the second month of life which means that almost 80% of the adverse events occurred during the first 2 months. Therefore, careful monitoring is particularly needed for this period [67].

3.5.2 Effect of Medications on Milk Production

Prolactin released from the anterior pituitary gland is the most important hormone that provides milk production. Drugs may cause an increase in milk production through dopamine-blocking actions which result in stimulation of prolactin production and release. Amisulpride, phenothiazines, and risperidone are antipsychotics with potent dopamine-blocking actions which may cause galactorrhea [63]. In addition TRH, serotonin, vasopressin, oxytocin, prostaglandins, opioids, histamine, and noradrenaline stimulate prolactin secretion [68]. On the other hand, drugs may interfere with the milk production through decreasing prolactin release or local blood flow to the breast tissue. Bromocriptine, cabergoline, ergotamine, estrogens, and pseudoephedrine can cause a reduction in breast milk supply.

3.5.3 Calculating and Interpreting Infant Exposure

3.5.3.1 Milk Plasma Ratio (*M*/*P* Ratio)

Milk plasma (*M*/*P*) ratio is the comparison of milk and maternal plasma drug concentrations. This ratio lets us to determine the dose of the ingested drug by the infant and whether the amount of drug being exposed is within the therapeutic range via the average amount of milk (150 mL/kg/day) taken per day of the infant. A *M*/*P* ratio >1 indicates that the medication passes to the milk in high levels, whereas a *M*/*P* ratio <1 indicates that the medication has passed to the milk in low levels [66]. For instance, the concentration of SSRIs, tricyclic or other antidepressants such as bupropion, nefazodone, and venlafaxine, in the milk is between 1% and 10% of the maternal plasma concentration [69].

3.5.3.2 Relative Infant Dose

Relative infant dose (RID) is the key parameter to assess potential risks of medication use during breastfeeding for infants. RID is calculated by dividing the dose the infant ingests per kilogram bodyweight to the maternal dose per kilogram bodyweight and expressed as a percentage. Infant exposure is considered as minimal when the relative dose is below 2%, small when the relative dose is 2–5%, moderate when the relative dose is 5–10%, and high when the relative dose is above 10% [58]. If the RID <10%, breastfeeding is usually considered as safe [66] although infrequent cases of possible adverse effects in the infants are reported even with relative doses below but close to 10% such as aripiprazole. Nevertheless, breastfeeding does not need to be contraindicated during the maternal treatment with some drugs of which RID is above 10%, such as fluconazole [70]. The RID is above 5% for most neuroactive drugs because of their high lipid solubility.

3.5.3.3 Infant Plasma Concentration

Although it is an invasive and painful method, infant plasma concentration is the most direct method of evaluating infant exposure. It can be also used to assess a suspicious adverse reaction related with medication use during lactation in individual infants. An estimate of the average infant plasma concentration can be made using the following equation [71]:

$$Cp = F \times \text{daily concentration in milk} \times \text{daily volume of milk ingested/CL}$$

F is the bioavailability and CL is the clearance of the medication. A thorough discussion of the limitations of this method can be found elsewhere [71].

3.5.3.4 The Ratio of Infant Plasma Concentration to the Maternal Plasma Concentration

This ratio might be more advantageous in terms of minimizing the variables such as the bioavailability and the differences in clearances between the infant and the mother [71]. It would be more accurate for the medications with relatively long half-lives since the fluctuations regarding medication levels would be minimal. The WHO working group considers a medication unacceptable if a steady-state infant plasma concentration is greater than 25% of the lower end of the therapeutic concentration

range although this is the arbitrary cut-off point [71]. A ratio over 10% is accepted as a cause for concern by the American Academy of Pediatrics (AAP) [72]. The choice of the cut-off points and the time for the sampling (the effect of transplacental passage) are very important in the assessment of the data [71].

3.5.3.5 Lactation Categories

A lactation risk categorization system was developed by Hale et al. to determine whether a drug is compatible with breastfeeding [66]. Five categories are described as follows:

- L1, compatible: No adverse effects have been observed in the baby of many lactating mothers, or no increase in risk has been detected during controlled studies, or the oral bioavailability of the drug is absent or very low.
- L2, probably compatible: Studies with a limited number of lactating mothers have not found an increase in adverse effects, and/or evidence is far from possible adverse effects.
- L3, probably compatible: There are no controlled studies, but there is a possibility that adverse effects may occur in infants or minimal, non-life-threatening adverse effects have been reported in controlled studies. The drugs in this group should only be used if necessary, taking into account the risk-benefit ratio. Also new drugs that have no data about breastfeeding included in this group.
- L4, potentially hazardous: There is evidence that it is risky for infant or mother's milk production, but breastfeeding may be acceptable if the benefits of the medication are taken into consideration (if the mother cannot be treated with other medications which are compatible with breastfeeding in the presence of a life-threatening serious condition).
- L5, hazardous: Studies conducted with breastfeeding mothers have shown that there is a significant risk for infant, or the risk of harm to the infant is high. Breastfeeding while using these drugs is contraindicated.

3.5.4 Important Points to Consider for Medication Use During Lactation

Medication use during breastfeeding should be avoided unless it is necessary. If clinically indicated, the medications with more documented experience should be preferred to relatively new drugs. The risks and benefits of each medicine for the mother and the infant should be evaluated. Most drugs are compatible with breastfeeding because they do not reach therapeutic doses in the infant's plasma, but for some drugs, taking off breastfeeding for a few hours or to completely stop breastfeeding may be recommended. If possible, drugs with low oral bioavailability, short half-lives, high protein binding, or high molecular weight should be preferred [66]. Before the drug is administered to the mother, the infant's age and clinical condition should also be assessed. Medications that are safe to use in the infants

are generally safe to use in breastfeeding women. Infants should be monitored for the adverse effects similar to those seen in the mother for antiepileptics, antidepressants, and antipsychotics [66].

3.6 Information Sources Regarding Medication Use During Pregnancy and Lactation

Teratology information services (TISes) are the most important sources of evidence-based information regarding medication use during pregnancy and lactation since they provide an individualized risk assessment for the particular patients. TISes are important sources of evidence since they conduct prospective cohort studies. The European Network of Teratology Information Services (ENTIS) [46] and MotherToBaby (Organization of Teratology Information Specialists, OTIS) [45] are TIS societies, of which members in individual countries counsel thousands of patients regarding medication use during pregnancy and lactation every year. According to a survey conducted with practitioners in Melbourne, Australia, in 2009, most of the physicians (73%) stated that they used software programs or books in this subject as information sources and 51% of the physicians reach information by phone [73]. Reprotox® and TERIS are the most known online databases which require a modest annual fee for the membership. LactMed is a peer-reviewed online source with free access which focuses on drug use during breastfeeding [60] (Table 3.2).

Table 3.2 Information sources [74]

1. PubMed and other evidence-based databases
2. Review resources (a) Micromedex® Solutions (b) Reprotox (http://reprotox.org) (c) Clinical Teratology Web—TERIS, http://depts.washington.edu/terisdb/terisweb/index.html (d) LactMed, https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm (e) *Catalog of Teratogenic Agents* (13th ed.). Shepard TH, Lemire RJ, Baltimore, MD: Johns Hopkins University Press, 2010
3. Reference books (a) Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. Ninth edition. Lippincott Williams &Wilkins, Philadelphia, 2017. HİLAL BUNUN EN SON BASIM TARİHİNİ KONTROL EDER MİSİN? (b) Schaefer C, Peters P, Miller RK. Drugs during pregnancy and lactation. Academic Press; 3rd edition (December 10, 2014). (c) Koren G. Medication safety in pregnancy and breastfeeding: the evidence-based A-to-Z clinician's pocket guide. New York: McGraw-Hill Medical; 2007. (d) Koren G. Medication safety in pregnancy and breastfeeding. New York: McGraw-Hill, Health Professions Division; 2007.
4. Web sites of Teratology Information Service Networks (a) OTIS (Organization of Teratology Information Services) in the United States and Canada, http://www.mothertobaby.org (b) ENTIS (European Network Teratology Information Services), http://www.entis-org.eu

3.7 Conclusion

The risk assessment regarding psychotropic medication use during the perinatal period requires the critical appraisal skills that enable us to assess the up-to-date information emerging from observational studies. The decision whether to use the medication or not should be done on a case-by-case basis, weighing the possible risks of the untreated maternal psychiatric disorder on mother, fetus, and growing child against the possible adverse effects of the medication on fetus or child. The decision-making process should involve the patient, while the mutual understanding of physicians' and patients' priorities should be ensured.

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General Approach to Pharmacological Treatment: During the Perinatal Period

4

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4.1 Introduction

Clinicians are generally fearful to prescribe psychotropic drugs (PDs) during pregnancy or when a mother wishes to breastfeed her own baby. The main reason is due to the fear of risks that these drugs could have on the fetus development and on the breastfed baby. In early pregnancy, particularly during the first 12 weeks, the risk of inducing congenital major malformations (MMs) is obviously the main concern, while in late pregnancy the risks associated with PD exposure mainly concern the gestational adverse events (particularly preterm birth) and some neonatal complications after delivery. Another source of concern is the potential long-term impact that in utero exposure to these drugs may have on the infant's neurodevelopment. Moreover, also during postpartum period, there is a concern that breastfeeding a baby while taking PDs can negatively affect the infant's health. Overall, for each case, it should be suggested to carefully evaluate the risk/benefit when prescribing PDs during pregnancy and breastfeeding.

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In the last decade, several national guidelines, from the European and North American countries, have been produced, aimed at providing clinical recommendations for an appropriate management of these medications during the perinatal period.

In the UK those most recently published comprise:

(a) The *National Institute for Health and Care Excellence* [1]
(b) The *Scottish Intercollegiate Guidelines Network* [2]
(c) The *Consensus guidance on the use of psychotropic medications in pregnancy and postpartum*, by the British Association of Psychopharmacology [3]

A short practice guideline was also published in 2008 by the *American College of Obstetricians and Gynecologists* [4]. A recent guideline was produced in Denmark and published by Larsen et al. [5].

Furthermore, it has been well known that specific trials for establishing the therapeutic efficacy and the safety profile of PDs, during perinatal period, are quite few, as controlled randomized clinical trials (RCT) are not allowed in pregnant women or during breastfeeding. Therefore, recommendations, suggested by these guidelines, have extrapolated the clinical efficacy of these drugs from nonpregnant and non-breastfeeding women. On the other hand, according to the BAP consensus guidance [3], "this seems quite reasonable, as there is no evidence that the efficacy of psychotropics could be different in the perinatal period."

Nevertheless, as reported by the NICE [1] "No psychotropic medication has a UK marketing authorization specifically for women who are pregnant or breastfeeding. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The woman should provide informed consent, which should be documented," a statement that, even though appropriate from a medicolegal point of view, is a further reason of concern for clinicians who need to prescribe PDs in the perinatal period.

Wisner [6] appropriately emphasized that a woman in the perinatal period could be considered as the "last true therapeutic orphan," because, due to the ethical, medicolegal, and infant safety concerns during pregnancy and breastfeeding, few pharmacokinetic, pharmacodynamic, or RCT are conducted during the perinatal period. However, despite this understandable limitation, it has been documented that, in some European and North American countries, there was an increase in the prescriptions of PDs during pregnancy, particularly the *selective serotonin reuptake inhibitors* (SSRIs) [7, 8].

Some reasons can likely explain the increased prescription of such drugs during perinatal period:

(a) The high prevalence rate of "nonpsychotic mental disorders" during antenatal and postnatal periods
(b) The recommendations that untreated mental disorders should be timely and effectively treated to avoid several risks for the mother, the gestation, and the newborn
(c) The clinical experience that SSRIs are effective drugs in treating several psychopathological conditions during gestation and breastfeeding

In addition, among women of severe mental disorders (see below), non-pharmacological interventions, which should be always considered as first-line options in the perinatal period, can be only partially effective or ineffective.

4.2 Risks of Untreated Psychiatric Disorders in Perinatal Period

4.2.1 Risks of Adverse Pregnancy and Neonatal Outcomes

It has been well documented that mental disorders, particularly depression and/or anxiety, may develop or exacerbate during the perinatal period [3, 9].

Many studies in the last decade, including systematic reviews and meta-analyses, estimated the potential risks for the fetus, the infant, and the mother of untreated mental disorders during the antenatal and postpartum period. While most such studies focused on women with anxiety and/or major depressive disorders, less information is available for other psychopathological conditions such as obsessive-compulsive, bipolar, and schizophrenic spectrum disorders [8, 10, 11].

Untreated maternal anxiety and depression during pregnancy and postpartum have been associated with various adverse outcomes. It has been reported that newborns were found at risk of intrauterine growth restriction, low birth weight, low Apgar score, significant increase of cortisol and catecholamine levels, and other neonatal adverse reactions, as compared to newborns of women not affected by psychopathological conditions.

Severe depression and anxiety may be also associated with higher rates of preterm delivery and admission to neonatal intensive care units [12, 13].

It was also observed that the negative consequences of untreated maternal depression or anxiety may interfere with childhood development [14]. Higher impulsivity, maladaptive social interactions, and cognitive, behavioral, and emotional difficulties have been observed in infants of untreated mothers [14].

Pregnant women with affective disorders appear to be more likely to engage in high-risk health behavior, including smoking, use of illicit substance, and alcohol abuse, and it has been demonstrated to be at higher risk of developing preeclampsia and gestational diabetes. An original investigation conducted by McFarland et al. [15] have shown that untreated major depression during pregnancy negatively impacts the "maternal-fetal attachment," suggesting that the basis for poor "mother-to-infant attachment" in postpartum depression may have roots in pregnancy [15].

Finally, it should not be underestimated that pregnant women with a severe untreated mood disorder (e.g., major depression, bipolar depression, or mixed state) are considered more at risk of developing a postpartum depression, psychosis, and suicidality [16].

Even though suicide has been considered relatively rare during the perinatal period, in some severe mental disorders, a higher risk of suicidal

ideation, suicide attempt, or suicide has been reported. Therefore, psychiatrists should carefully monitor and early identify related clinical manifestations, potential risk factors, and alarm symptoms related to suicide, in order to provide an appropriate and timely psychological and pharmacological treatment [17].

A recent UK analysis reported that 1 out of 25 women aged 20–35 who commit suicide does it during the perinatal period. Furthermore, these women were twice as likely to be actively receiving mental health care [18].

4.2.2 Risks Due to Discontinuation of PDs

The decision to discontinue a pharmacological treatment (or simply reduce the therapeutic dose), before or during pregnancy, as well as after delivery, for the fear of adverse events for the fetus or the baby to feed, needs to be carefully evaluated and discussed with the mother, due to the higher risk of relapse/recurrence of mental illness in the perinatal period.

A large trial found that women who discontinued their antidepressant therapy relapsed significantly more frequently as compared to women who maintained their antidepressant use throughout pregnancy. In this study, 68% of women who discontinued their medication had severe depressive relapse compared with only 26% of women who maintained their medication; moreover, those who discontinued their medication were three times more likely to be hospitalized [19].

The risk of relapse or recurrence in women with bipolar disorder who discontinued their drug treatment, before or during pregnancy, was documented in an original follow-up study conducted by Viguera et al. [20]. Among bipolar women who discontinued versus those who continued the treatment with mood stabilizers, the risk of recurrence was twofold greater, median time to first recurrence was more than fourfold shorter, and the proportion of weeks ill during pregnancy was fivefold greater [20].

More recently, a meta-analysis including 37 selected studies confirmed that the risk of relapse in bipolar women was significantly higher among those who were medication-free during pregnancy (66%) than in those (23%) who used prophylactic medication with mood stabilizers [21].

The risk of a drug discontinuation has been also confirmed even in schizophrenic pregnant women, with a relapse rate after the discontinuation of an antipsychotic treatment of around 50%. Therefore, the higher relapse rate seems to strongly recommend a maintenance pharmacological treatment, during pregnancy and postpartum, among women with severe mental illnesses (e.g., recurrent major depression, bipolar disorder), in order to prevent the risk of an acute exacerbation or the recurrence of their mental disorders.

4.3 Critical Issues in the Evaluation of Safety of Psychotropic Drugs During the Perinatal Period

4.3.1 Critical Issues in the Evaluation of Safety of PDs During Pregnancy

Despite a quite number of studies evaluating the safety of PDs during pregnancy have been so far published, many controversies and limitations still exist among the results of such studies. Firstly, an important issue to be considered is that the use of PDs during pregnancy should be essentially considered a "marker" for a population of women with different risk factors from the general population of pregnant healthy women. In fact, it has been documented that obesity, diabetes, smoking, alcohol, and illicit drugs use are common in pregnant women with psychiatric illness and might represent risk factors for congenital birth defects and other adverse pregnancy outcomes [22]. Therefore, some studies, not necessarily investigating the underlying psychiatric illness and/or specific risk factors, may be helpful in evaluating the potential associations between PDs and outcomes, not strictly caused by exposure to drug itself, but likely determined by the abovementioned "confounding factors."

According to Chisolm and Payne [23], it would be appropriate to improve the quality of the research investigations in the field of perinatal psychiatry "to implement in different countries more centralized national birth registries, with better systems for having data on potential confounders."

Moreover, it should be as well noticed that most information concerning the risks of PDs in pregnancy derives from retrospective studies, with associated biases that this entails. Overall, it is more likely to be reported the occurrence of congenital MMs following drug exposure among women taking drugs, as they are usually more monitored by clinicians ("recall bias"). In general, increasing the screening program for malformations among infants exposed in utero to a drug can lead to an increased detection, also including minor malformations that usually may not be of clinical relevance.

Furthermore, the interpretation concerning an increased *relative risk* (RR/odds ratio) of specific malformation needs to be evaluated along with data of its *absolute risk* (AR), so that clinicians may evaluate the overall risk of drug exposure in the light of its clinical relevance [24].

For example, exposure to sertraline during the first trimester of pregnancy was found to be associated with a higher RR (about four times) of anal atresia. If we consider that anal atresia is a rare defect in general population (5 infants out of 10,000, i.e., 0.06%), the AR for a pregnant woman who takes sertraline can be 0.2%. Similarly, a meta-analytic study reported a statistical significant risk of cardiac septal anomalies (RR = 1.5) for infants of women treated with paroxetine; considering that the incidence of cardiac anomalies in a general population is around 1%, the AR for a newborn exposed in utero to paroxetine is approximately 1.5% [25].

On the other hand, it should be noted that other studies and meta-analysis did not report such risk [22, 26, 27].

Therefore, as a general approach, the results of the studies published on the risks of PD exposure in pregnancy need a careful clinical, statistical, and epidemiological evaluation, knowing that, in this wide literature, specific risks (e.g., cardiac malformation) have been found in some investigation but not in others; moreover, not all data "statistically significant" are always "clinically relevant."

4.3.2 Critical Issues in the Evaluation of Safety of PDs During Breastfeeding

During the postpartum period, breastfeeding is one of the major problems in women who need to be treated with PDs. It has been also well established by the recent WHO guideline [28] that breastmilk is an essential source of nutrition for the baby and that the infant should be exclusively breastfed for at least the first 6 months to achieve optimal growth, development, and health.

It is common practice that many mothers in maintenance therapy with PDs would like to breastfeed their baby; however, these mothers are rightfully concerned about the transfer of PDs into breast milk and about the potential adverse effects that such medications can induce to a breastfed infant.

Therefore, information on the safety profile of these drugs during breastfeeding is of great clinical relevance to assist clinicians in the management of such women.

A useful guide to obtain information on the safety of drugs (including PDs) during breastfeeding can be found in *Drugs and Lactation Database—LactMed* [29].

However, even in this large database, limited information exists for some drugs, particularly for drugs recently marketed. Moreover, most safety information comes from case reports or case series. In addition, the majority of such data generally apply to term and healthy infants, while very limited information is available in breastfed premature or sick infants.

4.4 General Approach in the Prescription of Psychotropic Drugs During the Perinatal Period

Planning the drug treatment and management for women affected by a psychopathological condition should be made before the woman becomes pregnant. Ideally, it would be desirable that all women affected by psychiatric disorders should be in a good mental health condition for at least 6 months before trying to get pregnant. Therefore, the treatment priority must be to keep the mother in a good psychological state during pregnancy as well as in the postpartum.

Considering that about 50% of pregnancies are unplanned, clinicians often need to make treatment decisions for patients who are already pregnant. Every case should be considered individually, with a careful evaluation about the risks and/or benefits concerning the prescription of a drug treatment. The patient's psychiatric history, severity of symptoms, response to drugs, and wishes regarding drug use in pregnancy and breastfeeding all play an important role in planning a course of clinical care during the perinatal period.

There is still the need to improve the management of women with mental disorders during perinatal period, in routine clinical practice. Furthermore, there is the need avoiding the stigmatization of these women, often considered as psychologically impaired for childbearing and parenting and sometimes improperly advised to not seek pregnancy.

In the following sections, a short list of the most relevant recommendations concerning the use of PDs during the perinatal period has been accurately provided, in order to help clinicians in the care of (a) women in treatment with PDs who are planning to have a baby, (b) women already pregnant and in maintenance therapy with PDs, and (c) women who wish to breastfeed their baby while taking PDs.

4.4.1 Recommendations in Prescribing PDs Before Pregnancy

- Current guidelines strongly advise that pregnancy should be always taken in consideration in the care of all women of childbearing age. This is particularly crucial in those with "severe and persistent mental illness" (SPMI), recently defined by the *US National Advisory Mental Health Council*, as mental disorders that have profound effects on family relations, educational attainment, occupational productivity, and social role functioning over the life course. These psychopathological conditions (including recurrent unipolar depression, bipolar, general anxiety, and psychotic disorders) can arise at first onset of pregnancy or can be exacerbated as result of significant physiologic and psychosocial changes occurring during pregnancy and in postpartum [30].
- Contraception and optimization of physical and mental health in potential future pregnancies should therefore be discussed at all stages of care, not just when a woman becomes pregnant.
- It is important that all women with a mental illness in their reproductive years would have the possibility to get information and advice as regards pregnancy from a specialist in perinatal psychiatry and psychopharmacology.
- Women already taking psychotropic medications for a long-term maintenance therapy should also be adequately informed about the high risk of relapse if the drug treatment is discontinued before and during pregnancy and in postpartum period. Such information should be focused on the severity of previous episodes of illness, severity of current episode, and family history of episodes in relation to childbirth. This is of great relevance when the drug prescribed has been associated with a potential risk of early teratogenicity, as in the case of some anticonvulsant mood stabilizers, particularly valproate, whose adverse effects (like neural tube defects) may have occurred before confirmation of pregnancy.

4.4.2 Recommendations in Prescribing PDs During Pregnancy

- As general rule, the psychopharmacological treatment during pregnancy should be reserved to women who have been affected by a SPMI; however, the combination of a pharmacological treatment (as add-on strategy), with an effective psy-

chotherapy, such as the cognitive-behavioral therapy or the interpersonal psychotherapy, is recommended in pregnant women who have only partially responded to previous psychological treatment.

- The management of mental disorders in pregnancy always requires an adequate clinical monitoring of fetal development and maternal mental state, with close liaison among the perinatal mental health professionals (i.e., obstetricians, pediatricians, and midwives). It is recommended that women treated with PDs should give birth in a general hospital in which there is a neonatal intensive care unit, to provide a timely and effective management of potential neonatal complications, like "poor neonatal adaptation syndrome" (PNAS), an adverse reaction reported in neonates exposed to SSRI late in pregnancy. It has been suggested that the discontinuation of treatment 2 or 3 weeks before delivery could avoid (or attenuate) the syndrome. However, this option needs to be better established; as in many cases, despite the drug discontinuation, such complication may still develop, even though in most newborns the symptoms resolve spontaneously from 1 to 3 weeks. In addition, the discontinuation of the drug treatment can pose the mother at risk of early relapse in a critical phase of gestation.
- It has been as well documented that formula-fed infants were more likely to develop PNAS than infants who were breastfed; therefore, breastfeeding should be always considered the first-line option, particularly among preterm newborns.
- It is not recommended to stop the medications suddenly after the discovery of pregnancy since this does not necessarily avoid the risk of congenital malformations and, in addition, may cause a relapse for the mother. It would be much better if the decision to maintain or stop the drug treatment is going to be taken after consulting a specialist in perinatal psychiatry, so that the mother (and her partner) can share the decision having updated information about the potential neonatal risks due to drug exposure, as well as about the risks of relapse in case of drug discontinuation. Therefore, clinicians must be careful in carefully obtaining a written informed consent, in which all available information concerning risks and benefits of drug treatment and nontreatment during pregnancy and postpartum are detailed. A written informed consent should be obtained to confirm the final decision, even if the proposed drug treatment has been refused.
- During gestation, the prescription of monotherapy is preferred whenever possible, and the dosage of the drug must be individualized, in order to find the "lowest effective dosage" for each case. It is not appropriate to prescribe "sub-therapeutic" dosages of PDs, as this may expose both the fetus to the risks of a drug and the pregnant to the risk of an early relapse.
- PDs with the largest up-to-date evidence of safety for the fetus (e.g., risk of malformations) should be preferred as first-line option; the previous response to drug treatment needs also to be considered in the choice of drug. For example, agents belonging to SSRIs should be preferred, as first-line option (if indicated), because their safety profile has been more studied during pregnancy than that of other antidepressant drugs.

- All changes between psychotropic agents (even if belonging to the same class) should be carried out before pregnancy, so, it is better to avoid switching medications during pregnancy, unless the benefits are likely to outweigh the risk; changing the drug once women are pregnant increases also the number of fetal exposure.

4.4.3 Recommendations in Prescribing PDs During Breastfeeding

- It is strongly recommended that neonates should be exclusively breastfed during at least the first 6 months of life to achieve optimal growth and development. Thus, clinicians should avoid (if possible) using formula feeding immediately after delivery in infants of women taking PDs, for the fear that these medications can be at risk for the infant. In fact, most drugs are not contraindicated during breastfeeding as their concentration in breast milk is very low or undetectable, such as some SSRIs (e.g., paroxetine or sertraline), some benzodiazepine (e.g., lorazepam), and some antipsychotic and mood stabilizers (like olanzapine).
- An updated guide for clinicians to get information about the neonatal safety of drugs (including PDs) during breastfeeding can be found in the abovementioned database (LactMed). This database contains information on drugs to which breastfeeding mothers may be exposed. It includes many data on the levels of such substances in breast milk and infant blood and the possible adverse effects reported in the nursing infant. Suggested therapeutic alternatives to those drugs are also provided, where appropriate. All data are derived from the available scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency. LactMed database is updated monthly and is free of charge.
- It is strongly recommended that breastfed infants whose mothers have been treated with PDs should be monitored for potential adverse reactions, such the abovementioned PNAS and in case of respiratory distress; this is particularly relevant in premature or sick neonates and in mothers taking more than one psychotropic medication or taking high dose of drugs.

4.5 Conclusions

There is a general agreement among specialists in mental health that during the perinatal period, a psychopharmacological treatment should be prescribed only in the case of women affected by severe psychiatric illness. However, it is reasonably to use PDs, as an add-on therapy, also in women with clinically relevant psychopathological conditions that have only partially responded to non-pharmacological treatments.

The decision to prescribe PDs during the perinatal period is complex, particularly in the antenatal period, and needs in each case a careful evaluation of the risks concerning the fetal exposure to such drugs and the risks of an untreated psychiatric

illness. In fact, there are several studies documenting that untreated maternal severe psychiatric illness during pregnancy is associated with poorer outcomes for the mother and the infant, including increased rates of preterm birth, low birth weight, substance abuse, and overall worse health status. The literature regarding the risk of an untreated psychiatric illness during postpartum is even stronger, with adverse outcomes including lower IQ, slower language development, increased risk of attention deficit hyperactivity disorder (ADHD), and increased risk of behavioral issues and psychopathological problems in the exposed offspring. These findings often seem to get lost in the debate of whether to use psychotropic medications during pregnancy.

Recent data from large and well-designed cohort investigations have established that most PDs may be considered relatively safe during early and late pregnancy, as well as during breastfeeding. Therefore, the decision to start, continue, or stop a psychopharmacological treatment, particularly during pregnancy needs to be taken by the mother and her partner, after having updated information about the potential infant risks due to drug exposure, as well as about the risks of early, and often severe, relapse in case of drug discontinuation. For these reasons, it would be recommended to consult a specialist expert in perinatal psychiatry and psychopharmacology, in order to take an evidence-based decision, particularly in those cases concerning drug treatments considered at higher risk in pregnancy and/or during breastfeeding and in women affected by severe and persistent mental disorders.

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Part II

Safety of Psychotropic Drugs During Pregnancy and Lactation

Antidepressants in Pregnancy

5

Sophie Grigoriadis and Miki Peer

5.1 Introduction

Treatment with antidepressant medications during pregnancy and their possible association with adverse outcomes for the offspring has been a topic of considerable debate in recent years. Expert guidelines recommend weighing the relative risks of potential adverse maternal, delivery, neonatal, and infant/child outcomes following antenatal antidepressant exposure against those that may result from untreated depression and anxiety during pregnancy. Adverse risks have been reported for both arms of the scale, and it is important to understand the magnitude and relevance of the effects for each arm. This chapter is focused on the reported adverse effects of antidepressants. The potential for such effects exists as these medications pass through the placenta and the fetal blood–brain barrier. Antidepressants have been detected in amniotic fluid, enough to calculate levels, with a wide range of cord/maternal concentration ratios with some significance [1–4]. Such effects have been reported in large-scale population-based studies and smaller studies and summarized in subsequent reviews and meta-analyses although the findings are not consistent which makes it clinically challenging for many treating pregnant women.

There are different potential risks of concern following in utero exposure depending on the timing during the gestational period; the central nervous system continues to develop throughout gestation, and thus, exposure at any time point can have adverse effects on this system in particular. Most described risks appear to be small; however, results need to be interpreted from observational studies, which limits our

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confidence in conclusions; results from randomized controlled trials are not available in this population. Confounds which are present in such studies limit our conclusions. Factors of concern include demographic ones such as maternal age and socioeconomic factors which are known to affect pregnancy outcomes, for example. One of the most important confounding issues is "confounding by indication"; maternal depression/anxiety during pregnancy can have fundamental effects on both the physical and emotional health of the offspring, but it is often not taken into consideration in design or statistical analysis examining potential adverse effects. Moreover further study design issues include the use of large population-based registries which are retrospective and are rich in terms of subject size but often lack control for confounding factors not only for psychiatric disease but also for the use of substances and other potential antenatal medical complications such as hypertension and diabetes, which again affect pregnancy outcomes on their own. Moreover, the accumulation of such data was not initiated to address the primary question of potential adverse effects from gestational exposure and thus may lack other important variables that may affect results. In particular, databases lack detail regarding when exactly the exposure occurred and if indeed the medication was taken as it was prescribed. Some studies require more than one prescription which increases the chance that the medication was actually used but not all. Ascertainment bias also plays a potential role as both mother and clinician may be more observant for potential adverse outcomes given there was exposure. With more frequent monitoring, outcomes that may have gone unnoticed in the past, which can have little clinical consequence, such as minor malformations, may be detected. Recall bias is also an issue as mothers who are dealing with adverse effects in their infant may be more liable to remember use of medication. Such issues would inflate the risk. Moreover, postnatal factors such as ongoing active maternal disease and negative maternal behaviors play a role in longer-term developmental effects on the offspring which must be controlled in studies assessing adverse effects of gestational exposure but again are not consistent.

This chapter is organized around outcomes with the use of meta-analytic results primarily but includes a description of key studies where possible. The majority of studies group the antidepressants for their primary analysis, and although there are pharmacological differences among the drugs, adverse effects are likely to be a class effect albeit it is not known if they are medication versus class specific. The most studied class is the selective serotonin reuptake inhibitors (SSRIs), and these are indeed the most commonly prescribed currently. This chapter focuses on antidepressants as a class, but specific drugs are briefly reviewed so that the reader can supplement with their own reading as desired.

5.2 Conception

Studies have investigated whether the use of antidepressants, mostly SSRIs, will affect the probability of conception (fecundability), but the majority of the evidence does not support a reduction in the probability. Nillni et al. [5] assessed 2146

women who had been trying to conceive, in a prospective cohort study. Antidepressants did not appear to affect fecundability. Rather severe maternal depressive symptoms, independent of antidepressant treatment, were associated with less of a probability to conceive compared with those women without depressive symptoms. Moreover, the rate of in vitro fertilization does not appear to be affected by SSRI use ($n = 829$), but non-SSRI antidepressants ($n = 52$) were found to be associated with reduced odds of pregnancy [6]. Others also noted no effect of SSRIs on in vitro fertilization pregnancy and live birth rate [7, 8]. There is some data however to suggest that male sperm morphology and count may be affected by SSRIs (Sertraline; [9]).

5.3 Spontaneous Abortion and Perinatal Death

The association of antidepressant use with spontaneous abortion and perinatal death remains controversial. Several studies have found associations, while others have not. A meta-analysis by Ross et al. [10] did not find a significant association (odds ratio (OR), 1.47; 95% CI, 0.99–2.17; $p = 0.055$) when examining studies of higher methodological quality based on review although earlier meta-analyses pooled to a significant association [11–13]. Recently published data do not support an association based on Asian women. For example, a population-based study from Taiwan found no increased risk of abortion (aOR = 1.04; 95% CI, 0.70–1.52) or intrauterine fetal death (aOR = 1.28; 95% CI, 0.56–2.94) associated with prenatal antidepressant medication use (and depression) [14]. An earlier study based on a large data set with 1,191,164 pregnancies found an increased risk for miscarriage following SSRI exposure in the first trimester. The risk was also higher for those women who discontinued SSRIs prior to pregnancy than those remaining on them. It was the women who used the medication but did not have depression/anxiety diagnosis temporally close to pregnancy that had a low risk of miscarriage during the first trimester compared to the women who had the diagnosis but were not treated with medication. Confounding by indication was highlighted by the authors as being relevant [15] here. Similarly, a study examining registry data from five countries (over 1,600,000 births) with 29,228 mothers using an SSRI antenatally found comparable risks after controlling for confounders (including illness) when compared to those not using medications ($n = 1{,}604{,}649$) for stillbirth, neonatal death, and postnatal death [16]. Cesta et al. [6] in a register-based cohort study of 23,557 women found those undertaking their first IVF cycle, depressed/anxious women who were prescribed SSRIs ($n = 829$), did not have statistically significant associations for decreased live births; those prescribed non-SSRI antidepressants ($n = 52$) showed reduced odds of live birth (aOR = 0.27; 95% CI, 0.11–0.68). Those women who achieved pregnancy (39.7%) had higher odds for miscarriage with exposure to non-SSRI antidepressants (aOR = 3.56; 95% CI, 1.06–11.9). Based on meta-analytic results and the newest studies, the risk for spontaneous abortion and perinatal death with SSRIs does not appear to be significantly associated with antenatal antidepressant exposure, but the relationship with non-SSRIs is not clear.

5.4 Congenital Malformations

The risk of congenital malformations following antidepressant exposure has been researched for several years. Although there was a concern for a cardiovascular signal, currently data provide little evidence that antidepressant exposure in utero is associated with an increased risk for congenital malformations for antidepressants as a group [17]. They do not appear to be major teratogens overall. Meta-analyses have found an increased risk of cardiac defects with antidepressants, and particularly for paroxetine. The results however are not consistent, and where effects have been found, the magnitude is small.

In a recent meta-analysis of 18 cohort studies, SSRI exposure during the first trimester was related to increased risk for cardiovascular malformations in the infant (relative risk (RR) = 1.26; 95% CI, 1.13–1.39) (with significant, moderate heterogeneity $I^2 = 54\%$) [18]. Further, examination of specific cardiac malformations showed significant associations between the first-trimester use of SSRI and atrial septal defects (ASD; RR = 2.06; 95% CI, 1.40–3.03, six studies) and for ASD and/or ventral septal defects (VSD; RR = 1.27; 95% CI, 1.14–1.42, 18 studies) but not VSD (RR = 1.15; 95% CI, 0.97–1.36, seven studies) [18]. This meta-analysis however did not always use the adjusted estimates but rather the crude ones, and thus important confounders may not have been addressed. Recent large studies tried to control for confounding by maternal illness and did not find significant associations [19, 20]. As an example, Huybrechts et al. [20] with a cohort study of 64,389 women found that after restricting the analyses to depressed women and adjusting for other confounds, there was no association of significance following exposure during the first trimester and cardiovascular malformations. A Nordic (Denmark, Finland, Iceland, Norway, and Sweden) population-based study by Furu et al. [19] including 2.3 million live singletons and 2288 sibling pairs who were discordant for exposure to SSRIs (or venlafaxine) found significantly increased risks for birth defect, cardiac birth defects, atrial and ventricular septal defects, and right ventricular outflow tract obstruction defects following SSRI (or venlafaxine) exposure, but each sibling-controlled analysis decreased the association to nonsignificance indicating that the drugs themselves are not the major factors. Likewise, confounding by maternal depression has been suggested as a limitation of many earlier cohort studies.

In a reanalysis of data from the Quebec Pregnancy Cohort, Bérard et al. [21] compared antidepressant exposure in the first trimester to pregnant women with untreated depression (rather than healthy women, as is usually done in cohort studies). They report that for major congenital malformations, only citalopram was found to be related to an increased risk (aOR = 1.36; 95% CI, 1.08–1.73, 88 exposed cases). Other specific antidepressants were associated with specific types of malformations (see individual antidepressant sections; [21]).

In a recent nationwide study from Denmark, the risk of Hirschsprung's disease (caused by a rare congenital malformation of the gastrointestinal tract) was recently found to be increased in women who redeemed a prescription for SSRIs in the period from 30 days prior to conception to the end of the first trimester (aOR = 1.76; 95% CI, 1.07–2.92) and further increased when two or more prescriptions were

redeemed (aOR = 2.34; 95% CI, 1.21–4.55) [22]. This study needs to be replicated and confounding by indication was possible as well as confounding by unknown environmental factors that may be associated with this disease.

5.5 Delivery Outcomes (Preterm Birth, Birth Weight, Low Birth Weight, Gestational Age, APGAR Scores)

5.5.1 Antidepressants

There is multiple meta-analytic evidence of an increased risk for preterm birth (<37 weeks gestation), lower gestational age, birth weight, and APGAR scores following exposure to antidepressants in utero; the effects, however, are typically small and within the normal range [10].

5.5.1.1 Preterm Birth

This is commonly defined as birth before 37 completed weeks of gestation. A meta-analysis of 41 studies pooled to an increased risk for preterm birth in women using antidepressants at any time during pregnancy (aOR = 1.53; 95% CI, 1.40–1.66); those using antidepressants during the third trimester of pregnancy (12 studies, aOR = 1.96; 95% CI, 1.62–2.38; high heterogeneity) had a higher risk which remained when controlling for diagnosis of depression [23]. Of note, the association between preterm birth and first-trimester exposure was not significant (eight studies, aOR = 1.16; 95% CI, 0.92–1.45) [23]. Another meta-analysis of 28 studies also reported a significant association between prenatal antidepressant use and preterm birth (RR = 1.69; 95% CI, 1.52–1.88; moderate heterogeneity). Both SSRIs (18 studies, RR = 1.74; 95% CI, 1.52–2.00) and other antidepressants (10 studies, RR = 1.63; 95% CI, 1.38–1.93) were significantly associated [24].

A large population-based study from Italy found that antenatal antidepressant use was related to an increased prevalence of preterm birth (20%; 95% CI, 10–40%) when compared to women without antidepressant use in pregnancy or in the 9 months prior to pregnancy but not when compared to those who used an antidepressant just before pregnancy (and discontinued in pregnancy; i.e., depression drove the association rather than antidepressant use) [25]. This was true and of similar magnitude when considering SSRIs or other antidepressants separately [25]. Significant associations have also been found in Asian women (5064 with depression, 20,024 without depression); prenatal medication use and depression were related to an increased risk of preterm labor/delivery (aOR = 1.33; 95% CI, 1.04–1.70, $p < 0.05$) (7.2% in depression and medication vs. 5.4% in non-depressed; [14]).

The meta-analysis of 15 studies pooled to shorter gestational age for those infants exposed to antidepressants but noted the difference in mean gestational age between infants exposed and unexposed to the medications was about 3 days, which was argued as not likely to be clinically significant [10]. The mean difference of about

3 days was also reported in a following study [26]. Roca et al. [27] found dose was important—those with exposure to high dose of SSRIs were likely to have premature infants (OR = 5.07; 95% CI, 1.34–19.23).

Not all studies have found a significant association. Malm et al. [28], in their large study of 15,729 exposed infants (versus 9652 unexposed to medication but exposed to psychiatric illness or 31,394 infants unexposed to either), did not find a higher rate of preterm birth in the medication-exposed group as compared to either control group (exposed to psychiatric illness, unexposed to medication or illness). There were more preterm births in the psychiatric illness exposed group compared to the unexposed group; this argues for the illness having an effect on preterm birth and not the medication.

5.5.1.2 Low Birth Weight (Typically Defined as <2500 g at Birth)

A meta-analysis of 15 studies found a significant link between prenatal antidepressant use and low birth weight in the infant (RR = 1.44; 95% CI, 1.21–1.70), but there was significant heterogeneity (I^2 = 62%) which was due, at least in part, to whether the comparison was made to a control group with or without depression [24]. In a previous meta-analysis of 20 studies, birth weight was lower in those infants whose mothers used antidepressants than infants of mothers who did not use them [10]. The authors determined the mean difference between the groups to be 74 g, which they noted as small and not likely clinically significant. Furthermore, in a comparison of depressed mothers who used antenatally antidepressants to those depressed mothers without antidepressant use (six studies), the association for lower birth weight with exposure was no longer statistically significant.

The large, population-based study from Taiwan found no association between prenatal antidepressant use and depression and low birth weight (aOR = 1.11; 95% CI, 0.76–1.63; [14]). The large population-based study from Italy found that prenatal antidepressant use was related to an increased prevalence of low birth weight (20%; 95% CI, 10–40%) when compared to women who did not use antidepressant in pregnancy or in the 9 months prior to pregnancy but not when compared to those who used antidepressants just before pregnancy (and discontinued in pregnancy, i.e., depression drove the association rather than antidepressant use; [25]). This was true and of similar magnitude when considering SSRIs or other antidepressants separately [25].

5.5.1.3 Low APGAR Score

Meta-analytic studies have found exposure to antidepressants is associated with lower APGAR scores. Fourteen studies pooled to lower APGAR scores (at 5 min) among infants exposed antenatally to antidepressants compared with unexposed [10], but as the mean difference was 0.2 points between the two groups, the authors concluded this was not likely clinically significant. A recent large study compared women experiencing psychiatric illness (typically depressive/anxiety disorders) during pregnancy and treated with SSRIs (second/third trimesters) to women with depression but not treated with medications. For neonates born to women who used medications, after adjusting confounders, APGAR scores (5 min) less than 7 risk

was significantly greater in the exposed group (OR 2.2; 95% CI, 1.7–2.7) [28]. The large population-based study in Italy reported exposure in utero was associated with an increased prevalence ratio of low APGAR score compared to exposure to antidepressants only before pregnancy (i.e., antidepressant discontinuation when pregnant) (PR = 1.63; 95% CI, 1.01–2.61), but the adjusted analyses were no longer significant (aPR = 1.56; 95% CI, 0.97–2.53) [29]. The authors reported the effect was likely attributable to the treatment rather than the disease itself.

5.5.2 Selective Serotonin Reuptake Inhibitors

5.5.2.1 Preterm Birth and Birth Weight

A recent meta-analysis of eight cohort and case–control studies (93,982 exposed to SSRI in pregnancy vs. 1,143,687 controls) found an increased preterm birth risk following prenatal SSRI exposure (11.6% vs. 5.2%, OR = 1.45; 95% CI, 1.24–1.68) [30]. This was attenuated when aggregating only studies that adjusted for confounders (n = 3 studies, 113,526 women) but was still significant (aOR = 1.24; 95% CI, 1.09–1.41). The relationship remained when the comparison was limited to studies comparing women with depression and SSRI exposure to women with depression but no SSRI exposure (i.e., treated with psychotherapy alone) (6.8–5.8%; aOR = 1.17; 95% CI, 1.10–1.25) ("17% increase in preterm birth") [30]. Huang et al.'s [24] meta-analysis (18 studies) evaluating SSRIs found an increased risk for SSRI exposure and preterm birth (OR 1.74; 95% CI, 1.52–2.00) and low birth weight (<2500 g, nine studies, OR 1.48; 95% CI, 1.22–1.79). The meta-analysis of eight case–control and cohort studies found antenatal SSRI use was associated with significantly lower birth weight (two studies, mean difference = −117.12 g; 95% CI, −125.99 to 108.24) [30]. Not all studies have found a significant association. The national registry study by Malm et al. [28], which identified offspring of psychiatrically ill women (with mostly depressive/anxious disorders) and compared them to offspring that were exposed to SSRIs versus those not exposed, found the preterm birth risk was lower in the SSRI-exposed offspring.

5.5.2.2 Small for Gestational Age

The large Italian population-based study reported exposure to SSRIs antenatally was not associated with increased prevalence ratio of small for gestational age, compared to exposure to SSRIs only before pregnancy (i.e., SSRI discontinuation when pregnant) (aPR = 1.01; 95% CI, 0.87–1.17) [29]. Sujan et al. [32] examining a retrospective Swedish cohort found first-trimester SSRI exposure was not associated with small for gestational age after accounting for confounding factors (OR, 1.09; 95% CI, 0.99–1.20) (but was for preterm birth; OR, 1.27; 95% CI, 1.20–1.35).

5.5.2.3 Low APGAR Score

The same study as above reported exposure to SSRI antenatally was associated with an increased prevalence ratio of low APGAR score compared to exposure to antidepressant only before pregnancy (i.e., antidepressant discontinuation when pregnant)

(aPR = 1.69; 95% CI, 1.02–2.79) [29]. Given the comparison group here, the effect appears to be attributable to the treatment rather than the disease itself.

5.6 Neonatal Outcomes

5.6.1 Poor Neonatal Adaptation Syndrome (PNAS) (or Poor Neonatal Abstinence Syndrome (NAS))

It is a collection of transient, short-term adverse effects observed in the neonate following exposure to a number of drugs including antidepressants. The syndrome is not well understood, and some have described it as a withdrawal or, perhaps, toxicity secondary to serotonin exposure given its similarity to discontinuation syndrome and/or side effects of serotonergic medications in adults [33]. Essentially most behaviors are interpreted as signs of behavioral dysregulation in the neonate. Signs included respiratory distress, tremors, jitteriness or shivering, irritability, high-pitched cry, sleep and wake disturbances, altered/poor muscle tone, agitation and restlessness, hypoglycemia, hypothermia, feeding difficulties, and seizures, among others. This syndrome has been observed in 5–85% of infants exposed to serotonergic antidepressants in pregnancy, and likely the wide variability reflects differing definitions of the syndrome [33]. The condition is generally conservatively managed and the infants are observed although severe outcomes have been reported with the necessary medical management. Prematurity may be a risk factor. Generally the signs resolve within days to 2 weeks although up to about 30 days has been reported [34].

The first meta-analysis that pooled various studies reporting transient/short-term neurobehavioral effects following delivery having had third-trimester exposure did not pool to a significant effect in the primary analysis. A secondary analysis with an additional study was significant (OR = 1.99; 95% CI, 1.43–2.77) [35]. A more rigorous meta-analysis pooling eight observational studies reported a fivefold increased risk of PNAS in infants exposed to antidepressants in utero (OR = 5.1; 95% CI, 3.3–7.9) as well as an increased risk of respiratory distress (OR = 2.2; 1.8–2.7; nine studies) and of tremors (OR = 7.9; 3.3–18.7; four studies) [33]. This meta-analysis conducted sub-analyses where studies evaluated infants only exposed during the third trimester as well as infants exposed throughout pregnancy, and all analyses were significant. Subsequently a further meta-analysis pooling five case–control and cohort studies found antenatal SSRI exposure was associated with neonatal respiratory distress syndrome risk (3.7% vs. 1.4%, aOR = 1.33; 95% CI, 1.14–1.56) [30].

Although severe signs are rare, a retrospective study with 228,876 pregnancies evaluated convulsions and found that during the first 2 weeks, there was an increased risk following SSRI exposure (OR 4.9; 95% CI, 2.6–9.5) (infants exposed were 6196) but not non-SSRI medications [36]. This study adjusted for many confounds including maternal age, maternal diagnosis of depression or anxiety or substance use, other comorbidities, and smoking during pregnancy. Exposure was

confirmed by evaluating those infants who have been exposed to mothers who had filled three or more prescriptions for an SSRI in the final trimester of pregnancy. Although an increased risk for convulsions was found, it is important to keep in mind that convulsions are not common; the authors estimated that "1 additional case of infant convulsion would be expected for every 117 women" (pp. e7) using an SSRI during the third trimester. A recently published large population-based study reported exposure to SSRI in pregnancy compared to exposure to antidepressant only before pregnancy (i.e., antidepressant discontinuation when pregnant) was not associated with increased prevalence of neonatal convulsion (adjusted prevalence ratio (aPR) = 2.28; 95% CI, 0.87–5.97) [29]. Exposure to any antidepressant was associated with increased risk for convulsion (aPR = 2.81; 95% CI, 1.07–7.36).

When the syndrome was first described, some recommended that the dose of the antidepressant be lowered or the drug to be discontinued all together before delivery to mitigate the risk of PNAS, but this is no longer recommended [37]. Neonates exposed earlier during gestation still showed signs following delivery [37, 38]. Time of exposure was not found to be an effect-modifying variable in a sub-analysis of a meta-analysis that compared studies where late exposure was confirmed compared to those where the exposure timing was not late or not clear [33]. Moreover, changing the antidepressant medication or discontinuing it will put the mother at increased risk for relapse/recurrence as the period right after birth is the highest risk time for relapse of psychiatric disease [39]. Breastfeeding may lower the risk of the syndrome although this is not clear. An earlier study found that exposed infants who are exclusively breastfed during the postpartum period still showed signs of PNAS [40]. A more recent study found that exposed neonates (n = 247) who were breastfed showed signs of the syndrome although at a lower incidence than neonates who were given formula (OR = 0.3; 95% CI, 0.1–0.7) [41].

5.6.2 Persistent Pulmonary Hypertension of the Newborn (PPHN)

Persistent pulmonary hypertension of the newborn is a condition that may be an extreme form of PNAS although this is not clear. PPHN has been described to occur in about 2 per thousand live births. Studies have been conflicting in their results, but the weight of the evidence appears to be for an effect. A meta-analysis of five observational studies that pooled effects for infants exposed to SSRIs in late pregnancy found the pooled risk to be significant for PPHN (OR 2.5; 95% CI, 1.3–4.7). Increased risk however was still described as small clinically (3 per 1000 infants) with approximately 350 women needed to be treated with SSRIs to lead to one additional case (NNTH). Of note an increased risk was found for late exposure. The meta-analysis with early exposure (three studies) was not associated with increased risk of PPHN (OR 1.2; 95% CI, 0.6–2.6) [42]. A more recent observational study did not find an association with PPHN. This was based on a large administrative database which compared antenatally depressed women using an SSRI during the

last trimester ($n > 65,000$) compared to depressed women with no antidepressant medication use ($n > 650,000$); both groups had a comparable risk of PPHN (OR 1.1; 95% CI, 0.9–1.3). This study not only controlled for depression by comparing depressed women, but confounders including age of the mother, chronic medical disease, and a range of other medications were controlled for by matching. This new data was then added by the investigators to the above meta-analytic data and the OR remained significant (OR 2.0; 95% CI, 1.1–3.5); however, there was much variability across the studies [43].

5.7 Infant Outcomes

A study using a propensity-matched cohort had the primary aim of assessing the impact of in utero SSRI exposure and maternal depression ($n = 27$) on brain development using quantitative neuroimaging matched to those unexposed to depression or SSRI ($n = 54$). There was also a group of infants whose mothers had a history of depression but did not use SSRIs ($n = 41$) and matched to those whose mothers did not have depression nor use SSRIs ($n = 82$). SSRI-exposed neonates had changes in their white matter microstructure that were diffuse. Infants whose mothers had depression but not treated with SSRIs did not differ from the matched group. Regional and global tissue volumes did not differ in any group comparisons. The authors concluded that the SSRI affected either the white matter development or other factors attributable to treated depression such as genetic factors and the severity of symptoms [44].

A further study found changes in microstructural development and cerebral metabolism in those neonates born prematurely (24–32 weeks) who had exposure to SSRI in utero but no evidence for effects on cognition, language, or motor function by 18 months of age. There were only 14 neonates in the exposed group (163 in nonexposed), and the study did try to control for variables known to lead to prematurity, maternal variables, and other factors. The study however was retrospective and initially designed to address another question and thus likely lacked adequate power, and important confounds may not have been controlled for [45].

5.8 Child Outcomes

5.8.1 Growth and Cognition

It has been difficult to study the long-term effects and tease apart the potential medication exposure consequences from genetic maternal/paternal factors as well as ongoing maternal depressive illness and environmental impacts. Unfortunately, many women continue to experience symptoms of depression into the postpartum period, and given that maternal–infant interactions are affected by this, child outcomes are also affected [46–48].

To date, studies have not found evidence that SSRIs have effects on the growth of the child [49]. Although the data is limited, there is a perspective observational study that assessed growth parameters until 12 months. The study involved three groups: one was exposed to both maternal depression and treatment with SSRIs ($n = 46$), the second was a group who was exposed to maternal depression but no treatment ($n = 31$), and the third group served as controls who was exposed to neither depression nor medication ($n = 37$) [49]. The parameters of weight, length, and head circumference were compared, and no significant differences were found among the groups.

Studies regarding cognitive function, such as language and intelligence, have also had inconsistent findings across them. Some found adverse effects in children up till age 6, while others have not, compared to children without exposure [50–52]. A systematic review included a total sample size of 280 children who had been exposed to antidepressants, compared to 291 children who were not exposed, and outcomes in terms of language and cognitive functioning were comparable. This review also compared infant temperament as well as behavior, and these outcomes also did not differ [53]. A study published after the review corroborated the findings and also did not find significant differences when comparing emotional symptoms, peer/social relationships, and behavioral symptoms such as conduct problems, hyperactivity, and inattention [54]. A study that compared those children exposed to SSRI, to SNRI (venlafaxine), and to depression with no treatment found that although children of mothers in the three groups had comparable intelligence scores, these were significantly lower than the children of mothers who neither had depression nor exposure to antidepressant medication. Although the study groups were small (less than 65 children per group), this study was interpreted as supporting the illness itself rather than the medication affecting cognition [55]. A prospective population-based study (Norway) compared offspring of antidepressant-treated mothers during pregnancy (SSRIs; $n = 28$), offspring of prenatally depressed but untreated mothers ($n = 42$), and offspring with no such exposure ($n = 33$). No differences were found for general cognition at 5–6 years between the groups [56]. In another study of over 179,000 children, while initially having found significance, antidepressant exposure in utero was not related with intellectual disability in the child, after adjustment for confounders. Results were similar regardless of whether SSRIs or non-SSRIs were examined [57]. El Marroun et al. [58], in a prospective population-based study, did not find SSRI exposure nor maternal depression during pregnancy to affect nonverbal cognition of the offspring. Executive function was assessed at 4 years, and nonverbal intelligence was evaluated at age 5 and neuropsychological function when the offspring were 7 years old.

Studies that have found adverse effects on cognition include a perspective observational study with a maternal sample size of over 51,000. Children who had antenatal SSRI exposure over a prolonged period of time ($n = 161$), at age 3, showed delay in their language abilities compared to those children without such exposure. Interestingly this effect was found to be independent of maternal depression antenatally and prior to pregnancy (OR 2.3; 95% CI, 1.2–4.4). When children of mothers with depression were examined for language competence at age 3, they were also found to have increased risk of delay (OR 1.83 (1.40–2.40)). It is known that postpartum depression and anxiety can affect child cognition. Although the authors

reported that the results remained in the same direction for those with anxious and depressive symptoms during the postpartum period, further details were not provided. Moreover they also acknowledge that although language competence was lower, "very few children would be classified as having clinically impaired language even after long-term prenatal exposure to SSRIs" [page 1629] [59].

SSRIs have been found to be associated with alterations in neurodevelopment of the fetus. For example, activity in the non-REM phase of sleep and increased motor activity have been reported [60]. The clinical significance of these findings is not clear. Others have suggested that the effect of antidepressants on the development of the fetal brain may be reversible or not dependent on when the exposure occurred, but this remains to be determined [61].

Motor skill development is another area that has been investigated for psychiatric medications including SSRIs. A systematic review found evidence for no overall effect based on the majority of studies [53]. A subsequent longitudinal study (166 mother–child pairs) with infants of prenatally depressed mothers who were using SSRI ($n = 41$) or depressed only ($n = 27$), compared to 98 whose mothers who had no such exposure, found no effect on long-term motor functioning but did note a transitory one. Infants exposed to depression and SSRI and infants exposed to depression alone were comparable, but there was a significant SSRI by time interaction, where motor scores at the 26- and 52-week follow-ups were lower in the medication-exposed group compared to those infants who were only exposed to depression; however, this was not the case at the 78-week follow-up [52]. Other studies however found worse gross motor functioning and social–emotional and adaptive behavior on infant development subscales in exposed infants [62] while some noted prolonged SSRI use was weakly associated with delayed motor development was a weak finding and not of clinical significance Eke et al. [31].

Note that psychomotor skill development delays appear to be transient and within the realm of normal. A recent study published data on 8359 mother–child pairs with 4128 children having complete data at age 5. A significant effect was found for late SSRI exposure in pregnancy compared to unexposed in terms of increased risk for anxious and depressed behaviors (adjusted beta = 0.50; 95% CI, 0.04–0.96). Exposure in early and mid-pregnancy was not significant. Both groups of mothers had depressive/anxiety disorders. Externalizing, social and emotional problems did not differ significantly between children who were and who were not exposed at any time to medication. The authors acknowledged unmeasured confounding may have played a role in the results [63].

5.8.2 Autism

The association between antidepressant exposure in utero and the development of autism spectrum disorders in the child has been a subject of recent investigation. There is evidence both for [51, 64–69] and against an association [70–72]. There have been seven meta-analyses to date to our knowledge which have largely used the same data (case–control and cohort studies), but had slightly different selection

criteria, methods of analyses, control for confounders, and examination of exposure windows [73, 74]. The first in a 2014 meta-analysis found a significant pooled effect (OR 1.81; 95% CI, 1.47–2.24) [75] supporting an association between exposure in utero and autism in the exposed child. In the second meta-analysis from 2016, while a significance for the overall analysis was found (OR 1.45; 95% CI, 1.15–1.82), when examined for offspring with mothers with psychiatric disorders, the effect for an association between antidepressant exposure and autism was no longer significant. The authors noted while there may be an effect, the confound of maternal illness is significant [76]. Another group that published in the same year found an increased risk (SSRI and non-SSRIs), but their preconception exposure to SSRIs analysis was also significant. Third-trimester exposure was not, whereas the first and second were [77]. Brown et al. [78], in their unadjusted analysis, found exposure to an SSRI at any point in pregnancy as well as in the first trimester was associated with increased risk of autism. However, only the first-trimester exposure remained significant after adjusting for maternal mental illness. It was concluded by the research team that the association between exposure and risk for autism was not clear because of potential confounding. The last meta-analysis which also investigated the effect of timing in pregnancy (six case–control studies with over 110,000 patients) found a significant pooled effect (OR 1.81; 95% CI, 1.49–2.20) which again was weaker but still significant when accounting for past depressive illness in the mother (OR 1.52; 95% CI, 1.09–2.12). Trimester exposure did not alter the significance of effect; however, when controlling for maternal depressive illness in the past, exposure in the third trimester was no longer significant. The use of antidepressants prior to conception was also found to be significantly related with autism spectrum disorders which indicates that indeed psychiatric illness is a major confounder [79]. Kaplan et al. [80] found that there was an association between SSRI exposure in utero and autism. The analyses with maternal psychiatric illness without the use of medication were also significant. Using an antidepressant but stopping 3 months prior to becoming pregnant was not related with autism in the mother's offspring following her pregnancy. Once again the conclusion involved confounding by the illness of the mother driving the risk of autism in the child by this team. The most recent meta-analysis found a significant pooled affect (OR 1.82; 95% CI, 1.59–2.10; $Z = 8.49$, $p = 0.00$) between the exposure of SSRIs in utero and offspring with autism spectrum disorder but did not investigate the association further [81]. Overall, it appears that the risk of autism spectrum disorders following antidepressant exposure in utero is very small if it exists at all. Although some meta-analyses found a significant association, this was typically attenuated when accounting for maternal psychiatric illness. Confounding by indication appears to be a major driving factor, as analysis with mothers who used antidepressants but then stopped them prior to conception was also significant. Depressed mothers may be more likely to have children who will develop autism spectrum disorders irrespective of environmental or other exposures. Indeed prior studies have found depressed women are more likely to have offspring with autism [82, 83]. Studies have typically evaluated SSRIs although other antidepressants and tricyclic antidepressant exposure have also been associated [65, 69].

A recent study using administrative data with close to 40,000 singleton births found 2837 pregnancies had been exposed to serotonergic antidepressants. Of these, 2% (95% CI, 1.16–2.6%) of the children did have autism spectrum disorder diagnosis. Initial analysis found exposed children did show a higher risk for autism spectrum disorder compared to unexposed in utero, prior to adjusting for potential compounds (incidence of 4.51 versus 2.03 per 1000 person-years). After statistically controlling for confounds ("inverse probability of treatment weighting based on a high-dimensional propensity score," p. 1546), the association between exposure and autism spectrum disorder was not significant (hazard ratio (HR), 1.61 (95% CI, 0.997–2.59)). Even after comparing children exposed in utero to their unexposed sibling, the association remained nonsignificant (HR, 1.60 (95% CI, 0.69–3.74)) [84]. Other studies published in 2017 also did not conclude there was an association but rather the medication is an indicator of risk but not causal [32] or is related to the underlying disorder [85] but not all [86]. Rai et al. [87] found exposure and the risk of autism to be associated even after taking into account maternal illness but only for those without intellectual disability [87]. This paper also examined antidepressant use by fathers and found that there was not an increased risk associated with autism. Siblings exposed, compared to those not exposed, to antidepressant medications were not found to be significantly different in the risk for autism spectrum disorder. These authors note that antidepressants would account for "about 2% of autism cases in this population" … "if the association was causal and no women with psychiatric disorders used antidepressants during pregnancy" (p. 4). Taken together, these newest studies do provide evidence for other factors and more work is still required to understand if the link is causal.

5.8.3 Psychiatric Conditions

The association between antidepressant exposure in utero and psychiatric symptoms in the child also continues to be debated. One of the important confounds stems from the shared genetics of the offspring with the mother but also because the mother may continue to experience psychiatric symptoms as the child grows. A large study (n > 14,400 pairs of siblings, Norway) which controlled for maternal psychiatric illness both during pregnancy and by examining siblings theoretically controlled for genetics and environment did not find strong evidence for an association between antidepressant exposure (typically SSRI) antenatally and psychiatric symptoms in the offspring. Symptoms operationalized as emotional reactivity, somatic complaints, sleep issues, and problems with attention or aggression were not significantly associated when the child was 18 months. However, at age 36 months, prenatal antidepressant exposure was associated with childhood anxiety symptoms. Interestingly a history of maternal major depression itself was associated with childhood behavioral problems after adjusting for many variables [88].

There is at least one study that has shown potential long-term benefit of exposure to antidepressants in utero. Data from a large study with close to 50,000 women (Danish) examining the effect of SSRI exposure on behavioral issues at age

7 indicated that it was the children who were exposed to untreated maternal depression during pregnancy that had higher risk of inattention, hyperactivity, and peer problems compared to those exposed to motors who were using antidepressants [50]. This study provides evidence for the deleterious effects of maternal depression and that its treatment may reduce the risk. By contrast, Liu et al. [86] did not find lower incidence of psychiatric diagnoses in the exposed group of children for various psychiatric disorders (32,400 children with psychiatric diagnoses overall, 15-year cumulative incidence, adjusted, 8.0% (95% CI, 7.9–8.2%, unexposed group) versus 11.5% (95% CI, 10.3–12.9%, discontinuation of antidepressant group), 13.6% (95% CI, 11.3–16.3%, continuation group), 14.5% (95% CI, 10.5–19.8%, new users of antidepressant group)). The group who were exposed to ongoing antidepressant use in utero had increased risk of various psychiatric disorders (HR 1.27; 95% CI, 1.17–1.38), compared to those whose mothers discontinued medication. The authors discussed that the risk is affected by the severity of the mother's underlying psychiatric condition (not just one disorder such as depression) in combination with medication exposure while in utero. The most severely ill women would more likely continue using medication and this group did have higher risk.

Attention deficit hyperactivity disorder (ADHD) has also been implicated as a possible adverse outcome following in utero exposure of antidepressants. A recent meta-analysis with seven studies and 2,886,502 children pooled to an adjusted rate ratio (aRR) of 1.39 (95% CI, 1.21–1.61) when comparing exposed to unexposed offspring in utero. However, a similar increased risk was found when comparison was between those who used antidepressants in the past and those that did not (aRR = 1.56; 95% CI, 1.25–1.95). Maternal psychiatric illness was related to ADHD in the offspring (aRR = 1.90; 95% CI, 1.47–2.45) as well. The sibling-matched analysis yielded insignificant results. Taken together, the authors concluded the association seen between antidepressant exposure in utero and ADHD is to some degree explained by confounding by indication [89].

5.9 Maternal Outcomes

While results have been inconsistent, large studies that controlled for maternal psychiatric illness did not find antenatal antidepressant use was associated with cesarean section delivery mode. Oberlander et al. [90] compared outcomes in women taking antidepressants and positive for depression to those of women with depression alone; the risks were not greater for the women with antidepressants. A large population-based study in Taiwan found an increased risk of hyperemesis in women using antidepressant medication in pregnancy (aOR = 1.19; 95% CI, 1.05–1.35, $p < 0.01$); however, this study also found this increased risk, of a similar magnitude, in pregnant depressed women who were not taking antidepressants [14].

As SSRIs have been associated with increased bleeding risk, especially upper gastrointestinal, researchers have assessed postpartum hemorrhage risk with inconsistent results. While Salkeld et al. [91] and Lupattelli et al. [92] did not find an

increased risk, Palmsten et al. [97] found an increased risk after adjusting for confounds previously linked to increased bleeding risk. Grzeskowiak et al. [94] found late exposure during pregnancy (aRR 1.53; 95% CI, 1.25–1.86) was not only associated with hemorrhage; it was also associated with increased risk of severe bleeding (≥1000 mL of blood) (aRR 1.84; 95% CI, 1.39–2.44). Women who had a psychiatric illness but did not use antidepressants did not have an increased risk (aRR 1.04; 95% CI, 0.89–1.23). Others have also found increased risk with third-trimester exposure [95, 96], but the data overall are limited and the clinical significance is uncertain.

The recent population-based study in Taiwan ($n = 5064$ women with depression, $n = 20{,}024$ without, $n = 1049$ for depression treated with medication, and $n = 4015$ for depression without medication) found no increased risk of gestational diabetes (aOR = 1.04; 95% CI, 0.86–1.26), preeclampsia/eclampsia (aOR = 0.84; 95% CI, 0.54–1.31), antepartum hemorrhage (aOR = 1.06; 95% CI, 0.85–1.31), and postpartum hemorrhage (aOR = 0.81; 95% CI, 0.56–1.17) in pregnant women with depression and prenatal antidepressant medication use [14]. Prenatal antidepressant use and depression were associated with caesarian section risk (aOR = 1.24; 1.09–1.42, $p < 0.01$) (39.2% in antidepressant and depression vs. 34.6% in non-depressed), chorioamnionitis (aOR = 2.23; 95% CI, 1.19–4.17, $p < 0.05$), placenta previa (aOR = 1.13; 95% CI, 0.95–1.34), or placental abruption (aOR = 1.03; 95% CI, 0.56–1.88) [14]. No association was seen between prenatal depression and antidepressant use and premature rupture of membranes (aOR = 0.98; 95% CI, 0.77–1.25), or vacuum extraction/forceps (aOR = 1.10; 95% CI, 0.89–1.36) [14]. The large Italian population-based study reported exposure to antidepressant in pregnancy was associated with an increased prevalence ratio of intrauterine hypoxia and birth asphyxia compared to exposure to antidepressant only before pregnancy (i.e., antidepressant discontinuation when pregnant) (aPR = 1.37; 95% CI, 1.08–1.73) [29] and thus is evidence for attribution to the treatment rather than the disease itself.

As with the other outcomes, studies have been inconsistent with regard to hypertensive disorders. Palmsten et al. [93] found the rate of preeclampsia was about 5% between women with treated (SSRI, $n = 19{,}000$) and untreated depression ($n = 59{,}219$). Preeclampsia occurred less often in women who took SSRIs (5%) than SNRIs (9%) or tricyclics (11%). Others also did not find significant differences [28], but Palmsten et al. [98] in an earlier study found a relative risk of 1.22 (95% CI, 0.97–1.54) with an incidence of 3% and 2% in women treated with an SSRI than unexposed to SSRI.

5.10 Other Adverse Outcomes

A population-based cohort study with a sample size of 734,237 identified 2438 children who had antidepressant exposure in utero and 5829 diagnosed with epilepsy over the follow-up period (about 7 years). Exposure to antidepressants was related to a 27% higher risk of epilepsy during childhood compared to

children with no such exposure (aHR 1.27; 95% CI, 1.05–1.54) and higher if the mother had a diagnosis of depression documented (aHR 1.71; 95% CI, 1.10–2.66) 6 months prior or during pregnancy. There was no significant risk if there was in utero exposure without a depression diagnosis during pregnancy; evidence for an effect for diagnosis or its severity have a role in the associations found [99].

5.11 Review of Adverse Risk for Specific Antidepressants

5.11.1 Fluoxetine

Meta-analytic results have been inconsistent with some suggesting an increased risk of malformation [100], while others do not [17, 101]. At least one meta-analysis found exposure during the first trimester was associated with cardiac malformation risk (14 cohort studies, OR = 1.60; 95% CI, 1.31–1.95) [101] although another did not find cardiovascular malformations overall increased [17] following exposure. If a risk does exist with fluoxetine exposure, the risk is small and residual confounding cannot be ruled out.

A recent meta-analysis of 16 cohort studies examining the congenital malformation risk reported fluoxetine exposure in the first trimester was related to an overall increased risk of major malformations (12 studies, RR = 1.18; 95% CI, 1.08–1.29), cardiovascular malformations (12 studies, RR = 1.36; 95% CI, 1.17–1.59), septal defects (seven studies, RR = 1.38; 95% CI, 1.19–1.61), and non-septal defects (five studies, RR = 1.39; 95% CI, 1.12–1.73) [102]. One important limitation of this meta-analysis is that most of the included studies did not control for important potential confounders. There were no other system-specific significant associations following in utero exposure to fluoxetine (e.g., malformations of the urogenital, respiratory, or digestive system) although the authors point out that these analyses were based on a small number of studies ($\leq$4 studies) [102].

Studies have not found fluoxetine is associated with increased risk of spontaneous abortion [103, 104] or antenatal hypertensive disorders [93] but has been associated with postpartum hemorrhage [97].

5.11.2 Paroxetine

This SSRI has been associated with cardiac malformations, but not all studies found an association. While not all meta-analyses have pooled to a significant effect, at least three meta-analyses found infants with paroxetine exposure in utero had a higher risk of cardiac malformations than the unexposed group [17, 100, 105]. The effect sizes however were small. Recent data based on outcomes of infants whose depressed mothers took paroxetine antenatally during the first 12 weeks ($n > 8000$) compared to those infants of depressed mothers (who did not take antidepressants

(n > 180,000)) did not find increased risk for cardiovascular defects. Potential confounders were matched in the groups [20]. Similarly, in a large study based on data from multiple countries, a significant association was not found [19].

A recent meta-analysis of case–control and cohort studies investigating first-trimester paroxetine use (alone) reported a significantly increased pooled risk of any major congenital malformations (15 studies, OR = 1.23; 95% CI, 1.10–1.38) and major cardiac malformations (18 studies, OR = 1.28; 95% CI, 1.11–1.47) compared to no prenatal paroxetine exposure (the latter increased slightly when restricted to 13 studies with adjusted estimates) [106]. An association was also found between paroxetine use and increased risk of bulbus cordis anomalies and anomalies or cardiac septal closure (eight studies, OR = 1.42; 95% CI, 1.07–1.89), atrial septal defects (four studies, OR = 2.38; 95% CI, 1.14–4.97), and right ventricular outflow track obstruction defects (four studies, OR = 2.29; 95% CI, 1.06–4.93) [106]. Similarly in a reanalysis of the Quebec Pregnancy Cohort, paroxetine use in the first trimester was found to be associated with cardiac defect risk (aOR = 1.45; 95% CI, 1.12–1.88) and VSD/ASD (aOR = 1.39; 95% CI, 1.00–1.93) compared to women with untreated depression [21].

It remains to be clarified if hypertensive disorders are related to paroxetine use as the study results are conflicting [93, 107], but postpartum hemorrhage likely is associated with paroxetine use proximal to delivery [97].

5.11.3 Sertraline

Sertraline was not thought to be correlated with malformations overall. A meta-analysis including six observational studies was negative [100], and two large subsequent studies also did not find an increased risk [19, 20]. However, a recent meta-analysis of cohort studies found first-trimester use of sertraline was associated with a 36% increased risk of cardiovascular-related malformations (12 studies; 6,468,241 women) and atrial and/or ventricular septal defects (eight studies) compared to no prenatal medication use. Specifically an OR of 1.36 (95% CI, 1.06–1.74) was seen for cardiovascular-related malformations, and an OR of 1.36 (95% CI, 1.06–1.76) for atrial and/or ventricular septal defects was found (moderate heterogeneity, I^2 = 64% and 62%, respectively). Most studies adjusted for potential confounders. No significant association was observed between first-trimester exposure to sertraline and congenital anomalies of the nervous system (five studies), the digestive system (five studies), the urogenital system (five studies), the musculoskeletal system (five studies), and the eye, ear, face, and neck (three studies), but the number of studies for each investigation was relatively small [108].

Sertraline appears to follow the same pattern as most of the SSRIs in that it appears to be associated with postpartum hemorrhage [97] but not with spontaneous abortion [104] nor hypertensive disorders [93].

5.11.4 Citalopram and Escitalopram

A recent meta-analysis of eight cohort and case–control studies (1,507,896 women) found no association between citalopram use in pregnancy and the risk of major malformations (OR = 1.07; 95% CI, 0.98–1.17) or cardiac malformations (six studies, OR = 1.31; 95% CI, 0.88–1.93) [109] in exposed infants. Various studies have found increased risks however. A recent one from Bérard et al. [21] found only citalopram was associated with increased risk of major congenital malformations (adjusted OR (aOR), 1.36; 95% CI, 1.08–1.73; 88 exposed cases). There was also an increased risk of musculoskeletal defects (aOR = 1.92; 95% CI, 1.40–2.62) and craniosynostosis (aOR = 3.95; 95% CI, 2.08–7.52). As the pattern of defects varied across studies that found increased risks of malformations [110–112], it has been noted that they likely do not indicate true risks [113, 114].

Studies have not found citalopram is associated with increased risk of spontaneous abortion [103, 104] and antenatal hypertensive disorders [107] but is apparently related with postpartum hemorrhage (relative risk 1.5; 95% CI, 1.1–2.0) [97].

Data for escitalopram, which is the *s*-enantiomer of citalopram, do not indicate increased risk for malformations [19, 100, 115], spontaneous abortions [103, 104], nor hypertensive disorders [93] but are positive for hemorrhage postpartum [97].

5.11.5 Other Antidepressants

Compared to the SSRIs, the other classes of antidepressants have been less studied. Typically, however, the same pattern of results has been found as the SSRIs and thus they are only briefly reviewed.

5.11.5.1 Serotonin–Norepinephrine Reuptake Inhibitors (Duloxetine and Venlafaxine)

These drugs also do not appear to be major teratogens [23, 100, 114, 116–118], but not all studies have been negative [21]. In terms of spontaneous abortions, the data have been inconsistent [104, 119, 120]. The association with hypertensive disorders antenatally also requires clarification [93, 98, 121–123] with differences in incidence between 8% and 12% of those women exposed compared to unexposed [121, 122]. The sample sizes are not large enough to enable definitive conclusions. As with the SSRIs, postpartum hemorrhage has been found following late pregnancy exposure to this class as well [97, 96, 124]. Venlafaxine has also been associated with preterm birth [125].

5.11.5.2 Atypical Antidepressants (Bupropion and Mirtazapine)

Bupropion also has a low risk of malformations if they exist [114, 118, 126, 127, 128]), but cardiac anomalies [129, 130] have been reported; absolute conclusions cannot be made as not all studies have found this [131]. It has been associated with spontaneous abortion [126] but not with hypertension [93, 122] nor

hemorrhage [97]. What stands out about bupropion is its potential association with ADHD. A study comparing this drug to SSRI exposure after controlling for confounding, including psychiatric diagnoses in the parents, found ADHD was more often found in the offspring following bupropion exposure than SSRI exposure or no medication (4.4%, 2.5%, and 2.5% of offspring, respectively) [132]. Given the small sample sizes, however, definitive conclusions cannot be drawn.

Data for mirtazapine are also comprised of small sample sizes. To date, this drug has not been implicated to be associated with malformations [133, 134]. Data with spontaneous abortions has not been consistent [104, 135], but it does not appear to be related to hypertension [93] nor bleeding [97]. Data on preterm birth has also not been consistent [134, 135], but it has not been found to be correlated with low birth weight [134] nor stillbirth [135]. PNAS has been reported comparable to other antidepressants [133], and negative adverse effects with regard to neurobehavioral development [136] have not.

5.11.5.3 Tricyclic Antidepressants (TCAs)

These medications are regarded as low risk for malformations overall based on meta-analytic results, but not all studies have been negative [106, 137].

Clomipramine has been found to be associated with increased risk of malformations in at least one study [137].

Rates of spontaneous abortions with TCAs have been found within the expected range [104], but elevated rates of hypertension [93, 98] and hemorrhage have been found [97]. More preterm births following TCA exposure have not been seen [100], but typical PNAS signs have been reported [137–140]. Negative adverse effects on neurodevelopment have not been found [48, 139, 141].

5.11.5.4 Monoamine Oxidase Inhibitors (MAOIs)

The data on MAOIs are very limited but that from animal studies have been noteworthy for fetal growth restriction [137, 142–144]. A recent case reported noted malformations [145], but others did not [143, 146]. Reis and Källén [137] have included MAOIs in their analyses but did not present separate data.

5.12 Statistical Versus Clinical Significance

As most of these studies, if not all, investigated risks using observational data, statistical significance does not necessarily imply clinical significance. Moreover with observational data, associations can be positive or negative; however, they do not imply causality. In the 2017 papers investigating autism, for example, three papers indicated that there is a positive association although the authors rightly noted that this does not necessarily imply causality [86, 87]. In this area of research, there are too many uncontrolled variables or confounds limiting our conclusions that cannot be taken into account. While there are many confounds that studies either try to control for by comparing exposed and unexposed offspring to medications in depressed women or adjust in the analysis for depression or other psychiatric illness

Table 5.1 Expert recommendations based on scientific evidence and clinical experience

The scientific evidence is evolving and often conflicting
Data on the adverse effects of antidepressant exposure during pregnancy on diverse outcomes are confounded by many variables limiting interpretations of results
The most important confound is the effect of the psychiatric illness which itself has potential effects on similar outcomes as those studied for antidepressants
Antidepressants do not appear to affect women's ability to get pregnant; SSRIs do not appear to be associated with spontaneous abortion
Antidepressants do not appear to be major teratogens and recent data do not support an association with cardiac anomalies after accounting for confounds
Antidepressant exposure in utero is associated with:
• A small effect on gestational age, low birth weight, preterm birth, and APGAR scores
• PNAS but typically the signs are transient and infants are managed conservatively. PNAS is not just associated with exposure in the third trimester; thus, stopping the medication may not decrease the risk and increases the risk of relapse
• An increased risk for autism spectrum disorders at first but the risk is decreased to nonsignificant levels after maternal psychiatric illness has been taking into account. It is uncertain if exposure in utero increases the risk overall of ASD (or ADHD)
• Antidepressants may or may not be associated with increased risk for psychiatric illness in the child overall; the question is difficult to answer as maternal illness cannot be detangled. Severity of maternal illness is an important consideration
SSRIs appear to be related with postpartum hemorrhage, but the clinical significance of this remains to be determined
Antidepressants have been associated with other negative maternal outcomes, but the clinical significance is also not clear
Antidepressants other than SSRIs have been less researched and sample sizes are small and conclusions are limited. SNRIs do not appear to be associated with malformations, and with regard to spontaneous abortions and hypertensive issues, it is not clear. Preterm birth has been reported. They are associated with a small risk of increased maternal bleeding following delivery
Bupropion is not teratogenic but may lead to increased risk of spontaneous abortion but not hypertensive issues nor bleeding
Mirtazapine data have been negative for malformations, abortion, stillbirth, low birth weight, maternal bleeding, or hypertension, while data on preterm birth have not been consistent
Data on TCAs appear to be much like SSRIs although less data are available
Psychoeducation is paramount; patients must be informed about the risks in order to make an evidence-based decision that is best for them and their family. Although this chapter is focused on the medications, the risks of psychiatric illness need to be considered carefully and weighted against potential medication adverse effects
Overall, patients with mild or no depressive/anxious symptoms about 6 months to one year prior to pregnancy may be candidates for stopping medications. However, women with a severe history of illness which has been recurrent, and especially if symptomatic, are not good candidates for stopping medications. Risk needs to be weighed considering all options, and each woman's weighting is individual where no one path fits all

and other confounds, which potentially results in the loss of statistical power with smaller sample sizes, one that may have implications that affects the above is the severity of the illness. The area is devoid of evidence for efficacy in this population and thus we typically rely on data obtained from other phases of the life cycle. This is partially why such medications are recommended for women with severe disease.

However, women with severe depression and anxiety may have increased risk regardless. The effect of disease or other genetic factors may still play a role. Some studies may control for women with a depression history, which may address genetic factors, but those with active disease again may still have different risks than those with a history of the disorder which again may be related to illness severity at the time of evaluation [17]. Women with psychiatric illness must be treated like patients with any other medical disease during pregnancy as there are consequences for the baby, mother, and family as depression and other psychiatric disorders are not benign and must be given the same serious consideration as other medical disorders. No one questions to my knowledge if treatment should be withheld from an epileptic patient during pregnancy and psychiatric disease must be treated the same.

5.13 Conclusions

The scientific evidence on potential adverse effects following antidepressant exposure in utero is an evolving area and will remain a topic of debate as randomized controlled trials have not been conducted and likely will not be conducted in the near future. Most of the data, based on large populations with control for many confounders, indicates that these drugs are "relatively safe." Small increases in some risks also appear to result from the underlying maternal disease and this makes studying these drugs more difficult. In general, however, the potential benefit versus potential harms appears to lean toward using them to treat women with moderate to severe illness. A thorough review of all the potential risks is paramount with the mother and her family in order for a mutual decision to be reached and to prioritize the mother's health. The personal biases of the patient (and doctor) must be recognized and addressed. Furthermore, there often remains misinterpretation among treatment providers of the data and as a result significant undertreatment of depression in pregnant women. This chapter aimed to address this gap by reviewing the latest data with the hope that it is used to make balanced treatment decisions (Table 5.1).

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Antidepressants During Breastfeeding

6

Salvatore Gentile and Maria Luigia Fusco

6.1 Introduction

The American Academy of Pediatrics endorsed breast milk as the best and only source of nutrition necessary for the infant during the first 6 months of life [1]. A recent meta-analysis indicated that breastfeeding increases protection against child infections and malocclusion and intelligence and probably reduces the risk of overweight and diabetes in childhood, adolescence, and adulthood. Beneficial effects of human breast milk on infant health is associated with its peculiar components and, also, throughout epigenetic processes [2]. For nursing women, breastfeeding provides protection against breast cancer, improves birth spacing, and reduces the risk of ovarian cancer and type 2 diabetes. Moreover, breastfeeding provides a unique opportunity for bonding between infant and mother [3]. Benefits of breastfeeding for the baby, the mom, and the society are summarized in Table 6.1.

One potential barrier to meeting breastfeeding recommendations is concern about combining breastfeeding with medication use [5]. Because of the frequency of prenatal and postpartum depression [6, 7], the role of antidepressants is of particular interest. Compared to other psychotropic drugs (such as bupropion, trazodone, nefazodone, reboxetine, and vortioxetine), antidepressants have relatively well-documented safety profiles for breastfeeding mothers [8]. Specifically,

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Table 6.1 Breastfeeding

Benefits for babies	Benefits for moms	Benefits for the society
Breast milk is the most complete form of nutrition for infants A mother's milk has just the right amount of fat, sugar, water, and protein that is needed for a baby's growth and development Babies find it easier to digest breast milk than they do for formula	Nursing uses up extra calories, making it easier to lose the pounds of pregnancy It also helps the uterus to get back to its original size and lessens any bleeding a woman may have after giving birth	Breastfeeding saves on healthcare costs Total medical care costs for the nation are lower for fully breastfed infants than never-breastfed infants since breastfed infants typically need fewer sick-care visits, prescriptions, and hospitalizations
Breastfed infants grow exactly the way they should They tend to gain less unnecessary weight and to be leaner This may result in being less overweight later in life	Breastfeeding delays the return of normal ovulation and menstrual cycles	Breastfeeding contributes to a more productive workforce Breastfeeding mothers miss less work, as their infants are sick less often Employer medical costs also are lower, and employee productivity is higher
Premature babies do better when breastfed compared to premature babies who are fed formula	Breastfeeding lowers the risk of breast and ovarian cancers and possibly the risk of hip fractures and osteoporosis after menopause	Breastfeeding is better for our environment because there is less trash and plastic waste compared to that produced by formula cans and bottle supplies
Breastfed babies score slightly higher on IQ tests, especially babies who were born prematurely	Breastfeeding makes moms' life easier. It saves time and money They do not have to purchase, measure, and mix formula	
Breastfeeding can help a mother to bond with her baby Physical contact is important to newborns and can help them feel more secure, warm, and comforted	A mother can give her baby immediate satisfaction by providing her breast milk when her baby is hungry	
	Breastfeeding requires a mother to take some quiet relaxed time for herself and her baby Breastfeeding mothers may have increased self-confidence and feelings of closeness and bonding with their infants	

Benefits for the babies, moms, and society
Gentile [4]

Table 6.2 Expert recommendations based on scientific evidence and clinical experience regarding the use of antidepressants during lactation [13–21]

Approximately 80% of women experience maternity blues, but nearly 20% of such women blues will go on to develop major depressive episode in the first postpartum year
The prevalence of postpartum depression has been estimated as high as 14.5%
Although depressed mothers may prefer to avoid pharmacological treatment because of concerns about adverse effects in the nursing infants, it is important that postnatal depression is recognized and treated effectively as it may impair bonding between mother and child and enjoyment of an important period in the relationship
For mild or moderate forms of postpartum depression, non-pharmacological interventions should be preferred
For severe forms of postpartum depression, pharmacological intervention (or combined therapy) is mandatory
The decision-making process should be shared with the mother, after an evaluation of the risk/benefit ratios. In particular (a) risks associated with untreated maternal disorder, (b) benefits of breastfeeding, and (c) risk/benefit ratio of treatment
So far, among SSRIs sertraline and paroxetine are the medications with the lowest number of adverse reactions in suckling infants
Consider that primiparous women taking SSRI medications are more likely to experience delayed secretory activation, possibly through local 5-HT-dependent mechanisms
Among TCAs, nortriptyline is the medication showing the most reassuring safety data

selective serotonin reuptake inhibitors (SSRIs) are currently the first-choice treatment for postpartum depression [9–12]. Adverse effects of SSRI exposure during lactation have been reported in case studies, but large, controlled trials have not been conducted. Therefore, research on side effects is somewhat limited, particularly for long-term effects (Table 6.2).

The unresolved dilemma in the treatment of breastfeeding mothers is weighing the potential risk to the infant following antidepressant exposure through breast milk versus the disadvantage of not receiving mother's milk. A third alternative, to discontinue or not commence drug treatment, might be even more harmful, taking into account the risk of not receiving adequate treatment for the mother and thereby indirectly also for the infant [4, 22].

6.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

6.2.1 Fluoxetine

Since 1989, a relatively significant numerical information on the utilization of the drug in breastfeeding mothers has become available for fluoxetine [23–39]. The levels of fluoxetine in breast milk represented a significant predictor of the total infant serum concentrations [40]. The amount of drug transferred to an infant depends largely on the maternal drug concentration. Also, there is a stereoselective disposition of both fluoxetine and its metabolite, resulting in increased concentrations of the biologically active enantiomers in the infant compared with the mother [41]. Some case reports

suggest that fluoxetine exposure through maternal milk may induce severe neonatal complications [42, 43]. However, drug exposure started antenatally. Hence, it is likely that such reactions were due to the occurrence of the prenatal antidepressant exposure syndrome (PAES) [44] rather than exposure through maternal milk after birth.

6.2.2 Fluvoxamine

Available literature information on fluvoxamine use during puerperium is scarce, although quite reassuring [38, 45–51]. However, recently, a case of gastrointestinal symptoms in a neonate breastfed by a woman treated with low doses of fluvoxamine was reported [52].

6.2.3 Paroxetine

Exposure to paroxetine appears to be minimal for breastfed infants with respect to the resulting maternal serum drug levels [53]. Öhman et al. [54] found that the relative infant dose of paroxetine to a suckling infant is lower than that reported for fluoxetine and citalopram but higher than that reported for sertraline and fluvoxamine. The clinical effects of infant's exposure to paroxetine were evaluated in naturalistic studies and single case reports. Most such studies showed reassuring results [23, 40, 47, 55–61]. A retrospective study investigated the outcome of 42 infants breastfed by mothers treated with paroxetine [62]. Five patients (11.9%) reported adverse events in their infants. The most commonly reported adverse events in the infants were insomnia, restlessness, constant crying, and poor feeding. However, antidepressant exposure during pregnancy was not considered a criterion leading to the exclusion from the study. Hence, in this study too, it is likely that such reactions were due to the occurrence of the PAES [44].

6.2.4 Sertraline

In one of the first studies evaluating the amount of sertraline in the infants breastfed by mothers taking the medication, most breastfed infants had low serum levels of both sertraline and its metabolite, and only one infant showed relatively high medication levels [63]. Except for anecdotal reports of neonatal complications [64], data about the breastfeeding safety of sertraline seem to be quite reassuring. Indeed, more than few studies confirmed that sertraline concentration is very low in infant serum, although it may vary substantially over the 24-h day in breast milk [23, 36, 38, 47, 65–72]. Uguz and Arpaci [62] also evaluated 30 infants exposed to sertraline through maternal milk. Four patients (13.3%) reported adverse events in their infants. In the case described by Müller et al. [73], a preterm infant exposed in utero and via breast milk to sertraline showed signs of serotonergic overstimulation. The exclusively breastfed neonate recently described by Morin and Chevalier [74]

suffered from severe hypernatremic dehydration because of inadequate milk intake, with disseminated intravascular coagulation and right lower limb gangrene that required amputation of all five toes and surgical debridement of the metatarsals. The usual etiology of hypernatremic dehydration in this age group is insufficient breast milk intake. The infant's mother was treated for bipolar disorder with lamotrigine, aripiprazole, and sertraline 100 mg/day. An extemporaneous and, so far, unreplicated observation suggested that maternal sertraline treatment during puerperium may induce a temporary reduction in breast milk supply [75].

6.2.5 Citalopram/Escitalopram

Relatively significant numerical data regarding the utilization of antidepressants by breastfeeding women are also available for citalopram [23, 38, 76–83].

Escitalopram too is excreted into breast milk [84]. All the infants studied in this research exhibited normal behavioral and developmental milestones for age. The drug was below the detection limits in the infants studied by Ilett et al. [85], and they showed no iatrogenic symptoms. The total relative infant dose for escitalopram plus its demethyl metabolite was calculated at 5.3% [84]. The escitalopram absolute infant dose seems to be lower than that for the equivalent antidepressant citalopram [84]. In contrast, the study by Ilett et al. [85] in six mother-infant pairs found that the relative infant dose of escitalopram is similar to that reported for citalopram. In the case reported by Castberg and Spigset [86], the relative infant dose of escitalopram ranged from 5.1% to 7.7%. The mother did not report any adverse event in the infant. For a systematic review, see Bellantuono et al. [87].

6.3 Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

6.3.1 Venlafaxine

A low number of cases have been reported on venlafaxine [88]. Preliminary findings suggest no associations between venlafaxine exposure via maternal milk and unwanted repercussions on the infants [23, 89–92]. The relative infant dose expressed as a percentage of the maternal dose ranges between 4.1% and 10.8% [93–95]. It was also suggested that venlafaxine in breast milk could attenuate the noradrenergic-serotoninergic neonatal withdrawal symptoms in infants also exposed to the drug during the fetal life [96].

6.3.2 Duloxetine

Published information on duloxetine is anecdotal [88]. Lobo et al. [97] demonstrated that the drug shows detectable levels in breast milk, and steady-state concentrations in breast milk are about one fourth of those in maternal plasma. However,

this study was not designed to evaluate the estimated absolute daily duloxetine dose, and infants were not evaluated to assess the effects of duloxetine (i.e., pharmacokinetics and safety).

6.4 Tricyclic Antidepressants (TCAs)

All TCAs are excreted into breast milk [98]. Almost all of them are weak bases and would be predicted to have a milk-to-plasma (*M*/*P*) ratio greater than 1, a historical notional level of concern [99]. However, the clinical implications of this finding remain substantially unknown: in infants exposed to other classes of antidepressants, almost all unwanted reactions have actually been described when *M*/*P* ratios were lower than 1 [100]. Indeed, the relationships between the *M*/*P* ratio, the drug levels in the suckling infant's serum, and the degree of occupancy of specific neurotransmitter receptors in the infant's nervous system haven't been investigated.

6.4.1 Studies Investigating TCAs as a Group

The study by Nulman et al. [101] included a relatively large number of infants breastfed by mothers on TCA therapy. However, no information is available about the infants' outcome.

6.4.2 Studies Investigating Single TCAs

6.4.2.1 Imipramine

Studies on imipramine include case reports and case series, overall investigating 21 mother-infant pairs. Although only few serum concentration measurements were made [102–104], the clinical outcome for the babies was reassuring [103–105].

6.4.2.2 Desipramine

Seven infants have been described whose mothers were taking desipramine while breastfeeding, and no detrimental effects were observed [102, 104–106]. In six of these cases, plasma levels were found to be below the detection limit [105, 106].

6.4.2.3 Amitriptyline

Although the first case report on amitriptyline exposure via maternal milk dates back to almost three decades ago [107], there have only been seven additional cases reported since [104, 105, 108–111]. Secretion of amitriptyline and its metabolite into breast milk widely varies, depending on maternal dosage, time of investigation after parturition, and whether fore- or hindmilk was analyzed. Serum levels were below the limits of sensitivity in three infants [109–111]. Until now, there are no reports describing detrimental reactions in infants exposed to the medication through maternal milk.

6.4.2.4 Nortriptyline

Seven studies including a total of 28 cases investigated the safety of nortriptyline for the breastfed infant and showed no clinically adverse outcome [102, 105, 112–116]. In some of these cases, the levels of the parent drug and its metabolites in the maternal milk and serum, as well as in the breastfed infant serum, were measured. The infant's levels were either below the detection limits or very low.

6.4.2.5 Clomipramine

In the case-series study by Schimmell et al. [117], one baby was breastfed by a mother who continued clomipramine therapy during lactation. Maternal plasma and milk concentrations, the milk-to-plasma ratio, as well as infant levels, widely varied depending on the day of estimation after parturition. Although the baby's plasma levels were at some time points as high as the mother's plasma levels, no untoward effects to the infant were reported. Infant plasma levels were low in the infants reported by Yoshida et al. [104]. Where clinical outcomes were reported (8/10 cases), no adverse effects were observed [104, 117–119].

6.4.2.6 Dothiepin

Data are available on a total of 30 breastfed infants whose mothers were treated with dothiepin during lactation [104, 120, 121], but infant serum levels are only available in three cases. One infant had high levels of the parent compound and its metabolite [104], whereas in two infants, the serum levels were relatively low or below the detection levels [104, 120].

6.4.2.7 Doxepin

Two out of three single case reports described adverse reactions in infants exposed to doxepin through maternal milk [122, 123]. This finding may be due to the liability of active metabolite of doxepin to accumulate in the infant's serum; however, this finding remains controversial [124].

6.5 Other Antidepressants

6.5.1 Bupropion

Five studies (overall including 17 mothers and only eight infants) examined the excretion of bupropion in breast milk and the effects of the exposure to the compound on infants or toddlers [125–129]. The results indicated that the daily dose of bupropion and its metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion is relatively small. However, the possibility that bupropion might induce serious unwanted events in the suckling infants must be taken into consideration [127, 130]. Neuman et al. [131] actually discussed a case of seizure-like symptoms in an infant exposed to both bupropion and escitalopram through breastfeeding. In this case, the adverse event was associated with serum concentrations of bupropion and hydroxybupropion lower than the reported therapeutic range.

6.5.2 Trazodone/Nefazodone

Very limited (or no) literature data are available on trazodone and nefazodone [22, 132, 133].

6.5.3 Mirtazapine

One case report evaluated the utilization of mirtazapine by a breastfeeding mother [134]. The baby showed no unwanted events. The transfer of mirtazapine and its active metabolite into human milk and the dose to the infant via milk were calculated in a small sample size of mother-infant dyads. Mirtazapine was detected in only one of tested infants [135]. Given the minimal infant exposure to the drug and lack of adverse events in the case report by Klier et al. [136], breastfeeding continuation was allowed. In contrast to the cases hither to be published, Tonn et al. [137] found rather unexpected high infant serum levels that were almost within the adult therapeutic range. Their finding suggests that the individual differences in mirtazapine elimination rates in infants may be larger than could have been assumed. This infant had increased weight growth and slept better compared to its older siblings, which might be due to the exposure to mirtazapine through breast milk. In the case series described by Smit et al. [138], 44 infants were included who were exposed to mirtazapine via breast milk. No clinically relevant adverse reactions were observed.

6.5.4 Reboxetine

Only one study is available at the time this article was in progress. No reboxetine-associated adverse events have been reported to date [22, 139].

6.5.5 Vortioxetine

Available data in animals have shown excretion of vortioxetine/vortioxetine metabolites in milk. It is expected that vortioxetine will be excreted into human milk. At the time of writing, no human studies were available [140].

6.6 Conclusion

Despite the well-known severe repercussions of maternal depression on infants' well-being, women are often reluctant to seek pharmacological treatment for postnatal depression. The fear of adverse events for the suckling infant plays an important role in such maternal considerations. However, the pharmacological approach to mood disorders at postpartum onset often represents one of the most realistic options in a number of clinical conditions. Therefore, the necessity exists to

establish the safety of antidepressant treatment in the breastfed infant. For this reason, several years ago a specific safety index that assesses the frequency and degree of severity of adverse events in infants associated with maternal treatment with antidepressant medications during puerperium was proposed.

Unfortunately, the index is still underutilized both in literature and in clinical practice. Thus, a complete classification of antidepressants regarding their safety in infants nursed to the breast is unfeasible.

This situation indirectly highlights the limits of medical research in this field. Infants breastfed by mothers on antidepressant treatment should be still considered as "therapeutic orphans." Indeed, because of the lack of suitable published data, so far the index has been limited to the evaluation of five antidepressants. In accordance with the index classification for antidepressants, among SSRIs sertraline and paroxetine should be considered as first-line medications in women who need to start antidepressant treatment during the postpartum period and wish to continue breastfeeding [53, 138]. Data on nortriptyline are also quite reassuring [98]. Results from the recent study by Uguz and Arpaci [62] seem to confirm this evaluation for both paroxetine and sertraline.

The utilization of fluoxetine and citalopram seems conversely to be associated with a relatively higher risk of adverse events (with a low degree of severity, however) [53]. For the other newer antidepressant drugs, the index is still of no assistance to the patient or physician in deciding on the safety of their use in lactation [53].

Moreover, the study by Hale et al. [141] compared symptoms in mothers who took SSRIs while both pregnant and later breastfeeding to mothers who only took such antidepressants while breastfeeding. Mothers who took SSRIs while pregnant and then during breastfeeding were two to eight times more likely to report symptoms of discontinuation syndrome than women who took them only while breastfeeding. The overall rate of untoward reactions in infants exposed to SSRIs during lactation and not during pregnancy was surprisingly low (on average, about 10% of the mothers reporting symptoms). The most common symptoms were not particularly severe (irritability, low body temperature, inconsolable crying, and eating and sleeping problems) and occurred more frequently in infants whose mothers took medications with shorter half-lives.

Although preliminary data on the safety of some antidepressants are quite reassuring, new concerns regarding the use of such medications in lactating women are emerging. Primiparous women taking SSRI medications were more likely to experience delayed secretory activation, possibly through local 5-HT-dependent mechanisms [17]. Thus, medications that perturb serotonin balance may dysregulate lactation, and the effects are consistent with those predicted by the physiological effects of intramammary 5-HT bioactivity. For these reasons, mothers taking serotonergic drugs may need additional support to achieve their breastfeeding goals [17].

Hence, the decision to start or to continue antidepressant treatment in lactating women should be taken on individual basis, after a careful evaluation of the severity of maternal symptoms and weighing the risk for the mother-infant dyad of exposure

to mood symptoms against the risk for the baby of being exposed to antidepressant as "innocent bystander" [4]. Thus, non-pharmacological interventions should be taken into consideration when approaching women with mood disorders at postpartum onset. Promising findings exist for interpersonal psychotherapy, cognitive behavioral therapy, maternal-child interaction guidance, massage, and psychotherapeutic group support for specific parenting and/or child development outcomes [142].

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Antipsychotics in Pregnancy

7

Carolyn Breadon and Jayashri Kulkarni

Pregnancy and Antipsychotic Medications: Risks for the Mother

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7.1 Introduction

The changing patterns of antipsychotic medication use over the past 20 years have resulted in a dramatic shift in the typical profile of the pregnant woman taking these medications. Several decades ago, the use of first-generation antipsychotic medication was restricted largely to the treatment of women suffering schizophrenia and schizophrenia spectrum disorders. In more recent times, the use of second-generation antipsychotic medications has exploded, especially in North America, to treat patients with mood disorders (including bipolar disorders and major depressive disorders), anxiety spectrum disorders (including PTSD and OCD), ADHD, tic disorders, personality disorders and intellectual disability and developmental spectrum disorders.

Additionally, the use of first-generation antipsychotics in the past may have had the effect of reducing women's fertility through elevated prolactin, effectively arresting the cycle of ovulation. Second-generation antipsychotics do not have this tendency to the same degree, though case reports and clinical experience suggest that individual women may be sensitive to this effect even when taking medications not traditionally considered to be highly active at D2 receptors, such as olanzapine and quetiapine. Hence women taking antipsychotic medication are more numerous, more fertile and suffer a greater variety of underlying conditions which result in their use of antipsychotic medications in the contemporary era. These women could be encountered in any area of psychiatric practice.

Teratogenic risks of medications are traditionally considered to be at their highest in the first trimester of pregnancy, when women are often not aware that they are pregnant. This means that the care of every woman of childbearing age should incorporate a consideration of the risks of medication prescribed to a potential unborn child, and psychiatrists must be aware of these risks and communicate them clearly to their patients.

Once a woman is aware she is pregnant, her next consideration is a decision about the continuation of pregnancy. For this phase of care, a woman must be aware of the risks both to herself in continuing to take a medication throughout pregnancy which may affect her physical health and her experience of delivery and the risks to her child of congenital defects, adverse events at birth, or of later neurodevelopmental delay.

Again, it is the role of her psychiatrist to inform her of the risks of treatment to her and her baby, balanced against the risks of untreated illness including relapse in pregnancy or the postpartum. Women taking antipsychotic medications in pregnancy may be more vulnerable to metabolic effects including high rates of weight gain and gestational diabetes, particularly those taking second-generation antipsychotics [1–3]. Both weight gain and gestational diabetes have implications for delivery and neonatal outcomes.

Increasing evidence suggests that most antipsychotic medications do not confer a greatly increased risk of congenital malformations. However, babies may experience neonatal respiratory difficulties and medication withdrawal symptoms at delivery, suggesting that a neonatal ICU or special care nursery should be available.

Available data on neurocognitive development of babies exposed to antipsychotics in pregnancy seems to suggest that at 1 year there are no developmental distinctions between these babies and their peers [4, 5].

This chapter aims to provide a concise up-to-date summary of the known risks associated with antipsychotic medication treatment in pregnancy, to aid clinicians in providing best practice care to their patient (and by extension, to their patient's family).

7.2 The True Cost of Relapse in Pregnancy and the Postpartum

Women who are prescribed antipsychotic medications face a decision point when they discover they are pregnant. Anecdotally, many women cease all medications at this point. Recent evidence suggests that this is also true for women taking antipsychotic medications [6]. However, this decision can have serious consequences for the mother and also for her unborn or newborn child. Elsewhere, researchers have examined the dollar cost of a relapse of psychosis [7]. This can't begin to encompass the multiple problems associated with a relapse of psychosis for the individual and society in terms of financial, interpersonal, occupational and psychological costs. These costs are magnified and other risks are added in the context of pregnancy and childbirth. In clinical experience, treating a pregnant woman with psychosis in a general psychiatric inpatient unit provokes anxiety and distress for everyone involved in the woman's care, including the woman herself and her family. The risks are evident: fragmented antenatal care, poor attention to nutrition, itinerancy or homelessness, with all the risks to physical safety and health that these situations entail, including the need to commence higher doses of medication in hospital to establish, rather than maintain, a stable mental state.

It has been well established that women are at greater risk of relapse of mood disorders in pregnancy and in the postpartum, when this can manifest as postpartum psychosis. Women with a history of bipolar disorder who are untreated in pregnancy face a very high risk of relapse [8]. In the postpartum this relapse carries the added risks of suicide and infanticide [9], alongside the more subtle risks to attachment security and bonding which could occur through separation of mother and baby [10] or through the difficulties associated with bonding and psychosis [10].

Women with schizophrenia are perhaps uniquely vulnerable when faced with the challenges of parenting [11], especially when this is allied with other factors related to mental illness such as poor social support and economic disadvantage [12]. Howard et al. [13] lists the potential pitfalls for these women as follows: "Psychotic symptoms may affect the mother-infant relationship through involvement of the child in delusions, hallucinations or passivity experiences, by making the mother unavailable, or through the absence of desirable behaviours resulting in an impoverished environment for the child". These authors examined outcomes for unwell women with psychosis admitted to mother and baby units in the UK and advocated for early treatment of psychosis in averting parenting orders and family separation [13].

7.3 Evaluating the True Risks to Women and Their Babies from Treatment with Antipsychotic Medication in Pregnancy

The challenge in correctly identifying the true risk to a woman and her baby from treatment lies in unravelling the risks conferred by a medication from the risks associated with having a serious mental illness. A woman with schizophrenia or bipolar disorder may have genetic vulnerabilities shared by her child and may also have multiple vulnerabilities and disadvantages arising from the financial, social and occupational costs of living with a major mental illness. Taylor et al. [14] succinctly summarised the current state of research into confounding factors, writing "… the prevalence of these modifiable risk factors in these women is unclear as most studies have used clinical data from specialist services with limited generalizability, or have small clinical samples with limited statistical power to investigate differences between the groups, or have used administrative data of population cohorts with little detail on clinical characteristics".

7.3.1 Risks of Adverse Outcomes in Pregnancy Relating to a Diagnosis of Schizophrenia: Confounding by Indication

Jablensky et al. [15] examined the underlying risk relating to a diagnosis of major mental illness such as schizophrenia or affective psychosis on pregnancy-related, obstetric or neonatal outcomes in a population of women in Western Australia in the 1980s. They found that women with schizophrenia were significantly more likely to experience obstetric complications, and their babies to experience neonatal complications, than a comparison group without a psychiatric diagnosis. All women with a psychiatric diagnosis (included in this sample are women with diagnoses of schizophrenia, affective psychosis and unipolar depression) were significantly more likely to have a severe obstetric complication. Specifically, women with schizophrenia and bipolar disorder were significantly more likely to record placental abnormalities (placental abruption in women with schizophrenia, placenta praevia in women with bipolar disorder) and antepartum haemorrhage in women with bipolar disorder. Women with schizophrenia were significantly more likely to experience foetal distress in labour and their babies to require naloxone treatment at delivery.

In a clever analysis, Jablensky et al. [15] attempted to account for the differential effect of maternal mental illness and treatment by comparing cohorts of women whose first delivery occurred before, and after, their first psychiatric diagnosis. This showed a significant difference in cohorts. Women whose babies were born before their first diagnosis of mental illness (who were thus more likely to be provided treatment prior to and during pregnancy) were significantly more likely to experience obstetric complications. Women whose illness was diagnosed after their baby's birth had similar risk profiles to the general population. This pattern

remained when analysing cohorts of women with schizophrenia and with affective psychosis. The exceptions to this pattern were the risk of three specific obstetric complications, which remained significantly higher in the cohort of women with schizophrenia regardless of when they were diagnosed: placental abruption, low birth weight for age and cardiovascular birth defects. This difference could be accounted for by the influence of medication on obstetric and neonatal outcomes, or alternatively relate to severity of illness, which is often greater with early onset of disease.

Gentile [16] cited various studies to support the risks associated with major mental illness in pregnancy, including placental anomalies, eclampsia, antepartum haemorrhage, premature delivery, low birth weight and APGAR, shorter length at delivery, foetal distress, stillbirth, perinatal mortality and congenital anomalies [15, 17, 18]. This author specifically noted the correlation drawn between schizophrenia and major neurological malformations, preterm delivery, low birth weight and small-for-gestational-age babies.

Confounding by indication was further examined by King-Hele et al. [19] by looking specifically at markers of severity of disease (in this case, hospitalisation for psychiatric illness) and comparing the rates of adverse neonatal outcomes including stillbirth and neonatal death with these incidences in the general population. This group found a doubling in the relative risk of stillbirth due to mental health disorders in pregnancy and an even higher risk in those with alcohol and drug-related disorders (RR = 2.3, CI 1.2–4.2). Amongst women hospitalised with affective disorders, rates of congenital malformations were also much higher than in the general population (RR = 2.4, CI 1.1–5.1). Specifically examining women with schizophrenia and related disorders, there was a high risk of neonatal death due to fatal congenital malformations (RR = 2.2, CI 1.1–4.1). The authors discussed other potential contributors to these increased risks aside from the severity of illness, including associated lifestyle factors that themselves contribute to the rates of adverse outcomes. Kulkarni et al. [4] have also addressed this issue, using various assessments including the Positive and Negative Syndrome Scale and the Edinburgh Postnatal Depression Scale in pregnancy and postpartum, as well as the number of psychiatric hospitalisations as a proxy for illness severity in this group.

Reis and Kallen [20] addressed the problem of confounding by indication by investigating birth outcomes for all women taking antipsychotics, including those taking dixyrazine and prochlorperazine (commonly used for hyperemesis gravidarum). Thus these women were compared with women taking antipsychotic medications, both first and second generation, for their mental health. Notably, the women taking dixyrazine and prochlorperazine did not demonstrate an increase in rates of congenital malformations.

Habermann et al. [21] formed a contrasting view that as there does not appear to be a significant increase in rates of malformations in women taking either antipsychotic type, the underlying disease is unlikely to have an effect on the risk of congenital birth defects. Citing Sacker et al. [22] and Bennedsen [23], these authors write: “Because malformation rates in our study do not suggest a substantial teratogenic risk for second generation antipsychotics and first generation antipsychotics,

and mental illness is not supposed to possess a protective effect on malformation rates, we do not expect an undetected major influence of the disease on the risk of congenital birth defects".

7.3.2 Detection Bias

Habermann et al. [21] also raised the issue of detection bias, as women taking antipsychotics in pregnancy are often subjected to increased monitoring of all aspects of their care, both medical and psychiatric. These authors cited in support of this theory the detection of higher rates of isolated cardiac septal defects in their cohort treated with second-generation antipsychotics as opposed to the unexposed cohort, in which most babies affected by congenital abnormalities had multiple malformations. Habermann's group also suggested that postnatal adverse events such as low APGAR scores and foetal distress may relate to the underlying illness suffered by the mother, citing Jablensky et al. [15] and Matevosyan [24].

7.3.3 Confounding Through Social Change: The Risk of Long-Term Cohort Studies

Long-term studies that enrol women over the course of more than a decade risk cultural or historical factors intruding into their data. Increasing rates of obesity in the general population over time in England [25] or Canada [26], for example, could affect rates of gestational hypertension or diabetes in the sample taken a decade apart. Similarly, societal change in prescribing patterns, noted by many authors [27], could confuse results for large-scale studies which don't specify the type of treatment for a given mental illness. At the start of the 1990s, it might have been a typical antipsychotic; by the end of the millennium, it was overwhelmingly more likely to be an atypical.

7.3.4 Risks of Adverse Outcomes in Pregnancy Relating to Lifestyle Factors

Many studies have reflected this reality for women living with a mental illness. Women taking antipsychotics in pregnancy have been found to be more likely to smoke during pregnancy [1, 2, 4, 26] and to drink alcohol or use illicit drugs [1, 2, 21]. These women are also often older in their first pregnancy [20, 28] and more likely to be overweight [1, 2, 20, 28] with a lower educational attainment, higher rates of unemployment [20] and a higher rate of unplanned pregnancy [29]. These women were more likely to be single or not cohabiting with their partner [1, 2]. Many of the exposed cohort in the study by Habermann et al. [21] were nulliparous, consistent with other discussions on the effect of illness on fertility and decision-making around childbirth [15, 30]. Women seen in Kulkarni's [4] prospective cohort

had low attendance rates at antenatal clinics. Other studies have noted low rates of folate, prenatal vitamin and thyroid hormone use in pregnancy in women with mental illness [20]. Low rates of folate intake in at-risk populations with mental illness have been conjectured to contribute to higher rates of congenital birth defects in this group [21].

In addition to the genetic risks already discussed, Jablensky et al. [15] also note that risk factors for placental complications could occur in greater numbers in the cohort of pregnant women with mental illnesses; these authors specifically note factors such as older age (>35) and smoking, which could independently increase the risk of this outcome.

Habermann et al. [21] are the only authors to specifically screen for the use of folate as a confounder when comparing cohorts of women taking second-generation antipsychotics, first-generation antipsychotics and a matched comparison group. It was notable in this study that the rate of use of folate in pregnancy was markedly lower in both groups taking antipsychotics in pregnancy (85.7% and 85.2%) when compared to women not taking antipsychotics (95.5%), raising the possibility that there are other factors aside from increased rates of smoking, alcohol use and illicit substance use which may also increase the risk of congenital malformations in babies exposed to antipsychotic medication.

Similar to Habermann et al. [21], Sadowski et al. [26] found a lower rate of prenatal vitamin use in the group exposed to second-generation antipsychotics, at 87.6% compared with 99.2% ($p < 0.001$). Sadowski et al. [26] also found that the exposed women were much more likely to smoke and much less likely to breastfeed (both differences were statistically significant in this sample).

Taylor et al. [14] conducted one of the few studies to include domestic abuse as a factor in infant outcomes (low birth weight, small for gestational age or premature birth); however, these authors did not find a statistically significant difference in this measure in women with psychotic or mood disorders as compared with the general population in South London. Statistically significant differences between the two groups with serious mental illness included ethnicity (black African women were more likely to be diagnosed with a non-affective psychosis), smoking in pregnancy ($p < 0.05$), substance use in pregnancy ($p < 0.05$), age (women with non-affective psychoses were younger), level of recent acute psychiatric illness and single status. There was a high rate of ceasing or switching medications in both groups (40.4%). Both groups were substantially disadvantaged when compared with the general population, were substantially impaired in their general level of function (as measured by the HONOS) and experienced higher rates of domestic violence in pregnancy.

Nilsson et al. [31, 32] have examined the issue of confounding factors in assessing risk associated with antipsychotics from several angles. In 2002 this group demonstrated that increased risk for a woman with schizophrenia of having a baby of low birth weight was reduced from 80% to 30% when confounders such as smoking, low educational attainment and single status were considered. However, as the authors noted, a 30% increase in risk remained. In their subsequent [32] study, this group found that a diagnosis of schizophrenia made during an inpatient psychiatric

admission for either mother or father conferred an increased risk of more than twice for infant death. This association remained after controlling for covariates including age, parity, education, cohabitation and smoking. Considering the genetic factors in this association, the group then investigated whether the risk of infant death was higher amongst siblings of those with schizophrenia, but this was not the case. Very sadly, the researchers found an even higher risk of postneonatal death (OR 3.5) than neonatal death (OR 1.8) amongst the children of mothers with schizophrenia. These researchers also found a higher rate of low-birth-weight babies and small-for-gestational-age babies amongst children of fathers with schizophrenia, thus eliminating the moderating effect of antipsychotics in utero. Despite these findings, the authors felt that residual factors aside from genetics were likely to confer the bulk of risk for babies of parents with schizophrenia.

In a similar spirit, Ellman et al. [33] examined high-risk pregnancies in Finland, discovering that the babies of women with schizophrenia were at much higher risk of adverse outcomes including eclampsia, premature delivery, gestational hypertension, reduced birth weight (by 173 g) and reduced APGAR at 1 min (by less than 1) than other babies but that these women's siblings' babies were not at similarly elevated risk. These researchers found that maternal smoking was likely to be the factor which mediated low birth weight in babies of women with schizophrenia, though other adverse outcomes remained unexplained. The authors hypothesised that increased maternal age, maternal stress or other health risk behaviours such as poor nutrition, reduced vitamin use, limited prenatal care or substance abuse were the cause of adverse outcomes in the babies of women with schizophrenia, as their siblings did not show any of the patterns of elevated risk that these women did in pregnancy or the postpartum.

7.3.5 Polypharmacy in Pregnancy: The Rule Rather than the Exception in Women with Mental Illness and a Potential Confounding Factor Conferring Additional Risk

Most studies [1, 2, 4, 20, 21, 25, 26, 34–36] found that women taking antipsychotics in pregnancy were also taking multiple other psychiatric medications, often including antidepressants, anticonvulsants, lithium, benzodiazepines, anxiolytics/sedatives and opioids. Of those taking second-generation antipsychotics, 53.1% were also taking another psychotropic medication, as were 67.6% of those taking first-generation antipsychotics in the cohort examined by Habermann et al. [21]. The cohorts followed by Newham et al. [25] were similarly exposed to multiple agents including venlafaxine, nitrazepam, lithium, zopiclone, paroxetine, amitriptyline, sodium valproate, carbamazepine and cigarettes. The cohort examined by Sadowski et al. [26] overwhelmingly took more than one psychotropic, with polytherapy reported by 72% of women. Of these, 44% took two medications, 17% took three medications, and 11% took four or more. The most commonly used medications were antidepressants, benzodiazepines and anticonvulsants. In common with other

authors, Reis and Kallen [20] found that women taking antipsychotics for mental illness were much more likely to take other psychotropics, including anticonvulsants, benzodiazepines, sedative, hypnotics and antidepressants of all types.

Taylor et al. [14] found a high degree of polypharmacy in patients with both affective and psychotic illnesses, 44.8% in affective disorders vs. 38.9% in non-affective disorders. Of women taking more than one psychotropic, 21.1% of women with a non-affective psychosis were taking two agents, and 5.6% of women with non-affective psychosis were taking more than two agents in the first trimester of pregnancy. Of women with affective disorders taking psychotropics in pregnancy, 22.5% were taking two agents, and 8% were taking more than two agents in the first trimester.

Several studies discussed the uncertainty involved in various methods of ascertaining true rates of treatment, self-report or rates of filled prescriptions being two examples for which there must exist a degree of error. Newport took the further step of assessing cord blood at delivery to determine the percentage of placental passage of antipsychotic medications, correlating this with obstetric outcomes.

Risks associated with some psychotropics (benzodiazepines, anticonvulsants, lithium) are well characterised; risks associated with others (antidepressants) continue to be refined according to newer information. All of these add to the risk to which the pregnant woman and the developing foetus are exposed.

7.3.6 How to Identify the Confounders Which Have a True Effect on Adverse Outcomes?

The challenge in choosing confounding factors lies in correctly identifying these. Lin et al. [37] attempted to correct for confounders by excluding all women with a history of mental illness other than schizophrenia or bipolar disorder from their study, though it is unclear whether they also excluded women with schizoaffective disorder. They then excluded all women with partners who had a history of mental illness, as they felt this might also have an impact on the parameters studied: low birth weight, preterm birth and small-for-gestational-age infants. These researchers subsequently adjusted for gender and parity, maternal age, education, marital status, gestational hypertension or diabetes, father's age and education and family income, but not for smoking, alcohol intake, illicit drug use or body mass index (as noted by the authors). Lin also noted in their discussion that they did not assess smoking status, likely to be a major factor in preterm birth and low birth weight in women with a mental illness who have higher rates of smoking than the general population. However, Lin et al. [37] did note MacCabe et al. [38] who found that the relationship between bipolar disorder and low birth weight persisted even after adjusting for smoking.

However, despite our best efforts, confounding factors may exist which are highly likely to affect results but which remain masked or as yet unknown. Vigod et al. [39] attempted to address this problem by using high-dimensional propensity scoring (HDPS) in a carefully matched cohort from the general population not

using atypical antipsychotic medications in Ontario. This study matched women through their patterns of use of healthcare services, which much more closely mirrored the patterns of women taking antipsychotic medication. Fascinatingly, the maternal outcomes assessed (gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia and thromboembolism) did not appear to be significantly more common in the studied population, when using HDPS-matched comparison groups. Notably, even with the use of HDPS techniques, the matched cohort did not mirror the treatment group in all details, specifically in relation to polypharmacy. To manage this discrepancy, the authors subsequently adjusted for prescribed SSRI, non-SSRI, mood stabiliser and/or benzodiazepine prescribing during index pregnancy.

7.4 Issues Relating to Fertility for Women with Major Mental Illnesses

7.4.1 Fertility and Stress

It is established through animal- and human-based research that both mood and anxiety states can negatively affect fertility [40–44]. Specifically, stress, anxiety, negative life events and the experience of depression can all have a negative effect on fertility as measured by cycle-to-cycle rates of conception. It could be theorised that women taking antipsychotic medication may also fall into this category, as women with a diagnosis of schizophrenia or bipolar disorder are subject to the stress and negative life events related to the experience of a major mental illness.

7.4.2 Fertility and Major Mental Illness: Schizophrenia and Bipolar Disorder

It is also apparent that fertility may be reduced in women who suffer from schizophrenia and bipolar disorder related not primarily to their medication treatment but to their underlying illness. Multiple studies have observed lower fertility rates in those suffering from psychotic disorders [45, 46]. Laursen and Munk-Olsen [30] have demonstrated a similar trend in those suffering bipolar disorder, though those with schizophrenia were the most severely affected by low fertility rates in this study. These Danish researchers and others [15] have considered fertility to be a proxy measure for physical and mental wellbeing and thus a socioeconomic marker relating to the adversity experienced by those with mental illness. However, other researchers [37, 47] have attempted to tease out the clustering of adverse fertility indicators associated with major mental illness including poor diet, lack of exercise and obesity and have found that the increased risk of adverse pregnancy outcomes in bipolar disorder has remained. These researchers considered the possibility of an underlying genetic vulnerability in these women relating to the illness itself, rather than to the surrounding social consequences.

McKenna et al. [3] commented on the reproductive risks, including reduced fertility [41, 42], that women with psychotic illnesses face. These include unplanned pregnancies which may be unwanted [29], resulting in a higher rate of terminations [48], as well as a variety of other risks to the foetus such as higher rates of drug and alcohol use in pregnancy, reduced knowledge about contraception and increased rates of unplanned sex [49]. Kulkarni et al. [4] noted a rate of 7% of conceptions aided through IVF in their cohort of women with mental illness, approximately double the population rates of IVF pregnancy in Australia at that time.

7.4.3 Fertility and Antipsychotic Medications

Treatment with antipsychotic medication has traditionally been found to have a negative effect on fertility [50]. Historically this has been linked to the elevated prolactin level found in women taking first-generation antipsychotic medications [51]. More recently, risperidone seems to be the medication amongst the second-generation antipsychotics which causes the greatest rise in prolactin and hence suppresses ovulation [52]. Otherwise, the reduced effect of other novel antipsychotic medications on prolactin has been cited as a major reason why fertility rates in women with major mental illnesses appear to have risen over the past 20 years [53].

7.5 Obesity and Second-Generation Antipsychotics in Pregnancy

7.5.1 Obesity and Mental Illness

Molyneaux et al. [54] examined two studies which considered the connection between obesity and serious mental illness. The first, Ban et al. [55], noted a trend towards increased rates of bipolar disorder, schizophrenia or other psychotic illnesses in pregnant women with obesity, though this was not significant. Boden et al. [1, 2] noted a similar correlation, finding odds of bipolar disorder significantly higher for both obese and overweight pregnant women in comparison with pregnant women of normal weight.

7.5.2 Second-Generation Antipsychotic Medications and Obesity in Women with a Mental Illness

The most recent research would suggest that women with mental illness are especially vulnerable to antipsychotic-induced weight gain [56]. These views were anticipated a decade ago by Seeman [57]. In support of this conclusion, Seeman cited Koga [58], who found that the odds ratio for weight gain in women treated with antipsychotic medications for extended periods was significantly higher than for men, and Andersen et al. [59], who found that predictors for weight gain on psychotropics included the female gender.

Freeman et al. [60], using the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics, found that women were significantly more likely to have a high BMI prior to pregnancy if they were exposed to atypical antipsychotic medication than otherwise but that both groups gained a similar amount of weight in pregnancy. This amount was more than is recommended, suggesting that women with a mental illness may be more vulnerable to pregnancy-associated weight gain than otherwise.

7.5.3 Second-Generation Antipsychotic Medications, Obesity and Pregnancy

The risk of overweight and obesity for those taking second-generation antipsychotic medication is well known [61, 62]. Studies in women taking antipsychotic medication in pregnancy demonstrate that a heightened risk also applies in this subgroup. In one UK study [36], 16.5% of women taking second-generation antipsychotics prior to pregnancy (but who ceased before the first trimester) were obese in pregnancy. Rates of obesity increased to 22% in those who continued to take second-generation antipsychotics throughout pregnancy. These elevated rates were strikingly absent in the cohort taking first-generation antipsychotics either prior to or throughout pregnancy; in this group, rates of obesity ranged between 10.6% and 10.8%, comparable with rates for those who had never been exposed to antipsychotics, at 7.3%. These results are echoed by Habermann et al. [21], who also found a higher median BMI in women taking second-generation antipsychotics (24.2) than those taking first-generation antipsychotics (23.7) or those unexposed (21.8).

Sadowski et al. [26] noted that women taking second-generation antipsychotics in pregnancy were significantly more likely to be of higher weight than their peers, with mean pre-pregnancy weight of those exposed to second-generation antipsychotics at 74.3 kg and those unexposed at 64.6 kg, $p < 0.001$. Interestingly, there was very little difference in maternal pregnancy weight gain between the two groups. In their 2005 study, McKenna et al. [3] showed that women exposed to antipsychotics in pregnancy had a higher mean BMI by a large margin, falling within the obese range. Fifty-two percent of exposed women had a BMI of >27, in comparison with 29% of the unexposed group. This difference was significant ($p < 0.008$). Exposed women also gained more weight in pregnancy than their comparators, though this difference was not statistically significant. In contrast to other authors who have considered clozapine or olanzapine to be the most "obesogenic" [1, 2], quetiapine appeared to be the medication taken by the women with the highest BMI amongst the exposed group.

7.5.4 Obesity in Pregnancy and Risks to the Mother

Molyneaux et al. [54] commented on increased risks for women with obesity in pregnancy, including pre-eclampsia, gestational diabetes and foetal death, citing Sebire et al. [63]. There is substantial consensus on risks associated with

pre-pregnancy and pregnancy rates of obesity for gestational diabetes [64], gestational hypertension and pre-eclampsia [65], instrumental and caesarean section delivery [66] and wound infection [67].

7.5.5 Obesity, Second-Generation Antipsychotics and Mental Illness in Pregnancy: Risks to the Baby

In her editorial, Seeman [57] commented specifically on the risks associated with obesity in pregnancy, including to the foetus: increased risk of neural tube defects, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia and omphalocoele. This author cited theories as to the increase in rates of these anomalies in the context of obesity, including the possibility of undiagnosed diabetes in the obese mother, and suggested that the use of weight-inducing antipsychotics in pregnancy could lead to adverse outcomes from this mechanism alone, regardless of any direct teratogenic risk.

Gentile [16] noted the propensity for second-generation antipsychotics to induce obesity, especially in long-term treatment and in women of childbearing potential. He saw the risk of congenital malformations associated with pre-pregnancy obesity itself as an independent risk factor, suggesting that it may relate to undiagnosed diabetes (citing [68]). In his discussion Gentile also considered the longer-term risks of large-for-gestational-age babies, including later-life obesity, cardiovascular disease and diabetes (again, citing [68]).

Koren et al. [69] drew a link between obesity in pregnancy and the risk of neural tube defects, specifically in the context of the use of atypical antipsychotic medications, citing Werler et al. [70] and Shaw et al. [71]. This group observed folate intake of men (of whom 38% were obese) and women (of whom 63% were obese) with schizophrenia, compared with general population rates of obesity in Canada of 25% and 20%, respectively. This study established that levels of folate in the diets of people with schizophrenia are below those of the general population (23.2 nmol/L vs. 35.8 nmol/L). Koren's group suggested that both obesity and low folate intake present a risk for women with schizophrenia, who are also more likely to have unplanned pregnancies. Thus their babies are at risk from multiple factors in relation to congenital defects.

7.6 Gestational Diabetes

7.6.1 Gestational Diabetes in Women with Mental Illness

Hizkiyahu et al. [28] found that their cohort of women with schizophrenia had higher rates of gestational diabetes than their peers. Petersen et al. [36] found a strong association between obesity and gestational diabetes in women with mental illness, with an adjusted risk ratio of 5.49 (95% CI 2.67–11.2). Vigod et al. [72] examined a cohort of women with schizophrenia and found these women had a

higher rate of diabetes prior to pregnancy than an otherwise matched control group (3.9% vs. 1.2%). Subsequently adjusted odds ratio showed no significantly increased risk of gestational diabetes when women with pre-existing diabetes were excluded (OR = 1.13, 95% CI 0.90–1.44). This may reflect that women with a pre-existing diagnosis of schizophrenia have already commenced antipsychotic medication treatment prior to pregnancy, and their risk for development of diabetes has already risen. It is worth noting as previously that the same Canadian cohort, when compared with high-dimensional propensity score-matched comparison groups, did not have elevated rates of gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia or thromboembolism.

Boden et al. [1, 2] followed a group of women diagnosed with bipolar disorder who demonstrated a non-significantly increased risk for gestational diabetes; this tendency became more marked in the group receiving treatment. This study did not distinguish between mood stabilisers, considering lithium, antipsychotics, carbamazepine, lamotrigine and valproate in the same category when evaluating risk of adverse maternal outcomes.

7.6.2 Gestational Diabetes and Antipsychotic Medication Treatment: Prior to and During Pregnancy

In the 2013 study by Sadowski et al. [26], women exposed to second-generation antipsychotics in pregnancy were not significantly more likely to develop gestational diabetes than the control group. Note that this cohort was also exposed to multiple other psychotropics (though anticonvulsants were excluded). After excluding women with pre-existing diabetes, the study by Bellet et al. [73] found 4.7% of exposed women developed gestational diabetes compared with 4.1% of the unexposed group. Hence there was no significant increase in risk associated with the use of aripiprazole.

The second group studied by Boden et al. [1, 2] (women taking antipsychotics in pregnancy, of whom about half had a diagnosed psychotic disorder) were more than twice as likely to have gestational diabetes as the general population. After adjustment for confounders including birth order, maternal age, country of origin, cohabitation, smoking and height, these differences remained but were reduced in degree and lost significance in the group only taking olanzapine or clozapine (these were considered the most "obesogenic" by researchers).

Using the Massachusetts Birth Registry for Atypical Antipsychotics, Panchaud et al. [74] examined outcomes for gestational diabetes. They followed 303 women, compared with 149 controls not exposed to medications, not closely matched for demographics or diagnosis, with none of the reference group suffering a psychotic illness. Both groups had high rates of exposure to other psychotropics (72% in the exposed vs. 65% of the unexposed cohort), including SSRIs in 31% and anticonvulsants in 42% of the exposed cohort. Interestingly in the context of other studies discussed, this group did not find an increase in the risk for gestational diabetes in raw or adjusted terms (contrasted with Boden et al., [1, 2] Reis & Kallen [20], Petersen et al

[36]). These authors found that a more compelling predictor of gestational diabetes was *pre-pregnancy weight*, consistent with Molyneaux et al. [54], Sebire et al. [63] and Torloni et al. [64]. Panchaud et al. [74] did find a modest dose effect of medication in increasing the risk of gestational diabetes but found that this increased risk was also mediated by higher BMI. By contrast, Yeong et al. [75], examining women with a very similar profile through the Australian National Register of Antipsychotic Medications in Pregnancy, found extremely high rates of gestational diabetes in this population, at 22.1% compared with an expected population rate of 5.5%.

Consistent with research on other sedating antipsychotics, clozapine appears to confer an increased risk of gestational diabetes (OR 2.44 CI 1.14–4.24) in Mehta and Van Lieshout [76], citing Boden et al. [1, 2]. Mehta and Van Lieshout [76] also cite case reports of gestational hypertension, excess weight gain and anaemia scattered through the literature over the past 35 years [77–79]. However, women taking clozapine usually suffer more severe psychotic illnesses, and these women are already at risk of adverse outcomes in pregnancy. Unfortunately, as the frequency of these risks is so low, case reports cannot accurately differentiate the contribution of risk from illness as compared with its treatment.

7.6.3 Risks of Gestational Diabetes to the Mother

Vemuri and Rasgon [80] report on a case of gestational diabetes which they consider could have been directly worsened by olanzapine treatment, as the woman's blood glucose levels became more abnormal after increases in dose of olanzapine, despite no significant weight gain. They comment on the implications of using a medication which may have an effect on obesity, diabetes and insulin resistance, in the context of pregnancy, which itself increases the risk of insulin resistance.

Fascinatingly, Frise et al. [81] describe the case of a woman whose gestational diabetes they attribute in part to the commencement of olanzapine in pregnancy. This woman developed life-threatening ketoacidosis after an increase in her dose of olanzapine, a reduction in oral intake and the commencement of metformin. They note the autopsies of several patients treated with clozapine and olanzapine who seem to have died from catastrophic ketoacidosis and suggest that the combination of pregnancy as a hyper-insulin state, with olanzapine, known in animal models to affect glucose metabolism, should be undertaken with caution.

7.6.4 Risks of Gestational Diabetes to the Baby

Seeman [57] comments on the risks posed to babies from diabetes in pregnancy, presenting data that suggest an increase in risk of congenital malformations of OR 1.2 per unit increase in glycosylated haemoglobin [82]. This data also suggests that good, close glycaemic control is paramount in pregnancy and provides further support for close monitoring of all parameters for women taking antipsychotics in pregnancy (per [16]).

7.7 Gestational Hypertension and Pre-eclampsia: Embolic Events in Pregnancy

7.7.1 Gestational Hypertension in Women with Mental Illness

Vigod et al. [72] found that rates of gestational hypertension were higher in a cohort with schizophrenia (2.8% vs. 2.0%), having already excluded women with pre-existing hypertension. Amongst this group, women with schizophrenia were already at nearly twice the risk of those without this diagnosis (3.7% of women with a diagnosis of schizophrenia vs. 1.9% in the control group).

7.7.2 Risk Factors for Gestational Hypertension

Whilst not commenting on hypertension in pregnant women specifically, Seeman [57] notes that obesity can add to the risk of hypertension, especially in women.

7.7.3 The Risk of Pre-eclampsia for Women with Major Mental Illness

Similar to the finding by Vigod et al. [72] on hypertension, women with schizophrenia were at higher risk for pre-eclampsia in this study, with approximately double the rate of this complication in pregnancy (adjusted OR 1.84 CI 1.28-2.66). By contrast, Reis and Kallen [20] did not find a significant increase in the risk for pre-eclampsia in their sample of women treated for mental illness with both first- and second-generation antipsychotics.

7.7.4 Embolic Risk for Women with Major Mental Illness in Pregnancy

In her editorial on the differential impact of treatments for mental illness on women, Seeman [57] comments that the risk of stroke in women with schizophrenia has been found to be much higher than for male patients [37]. Supporting this assertion, Vigod et al. [62] demonstrated in a large population-based sample that women with schizophrenia were already at higher risk for embolic events prior to pregnancy, with rates more than three times higher than that of the control group (1.7% vs. 0.5%). In pregnancy this risk remained significantly higher in women with schizophrenia, with a doubling of risk for this group compared with controls: unadjusted odds ratio of 2.20 (1.36–3.55).

7.7.5 Embolic Risk in Pregnancy Relating to Antipsychotic Use

Seeman [57] further comments specifically on the effect of antipsychotics of both classes on the risk of thromboembolism. She cites studies showing a sevenfold increase of primary venous thromboembolism [83] associated with the use of antipsychotic medication and suggests that this risk must only escalate in the context of pregnancy, which is itself a period of higher risk of embolic events.

7.8 Obstetric Outcomes for Women with Mental Illness in Pregnancy

The 2014 study by Vigod et al. [72] showed women with schizophrenia at significantly greater risk for a variety of adverse outcomes including placental abruption, septic shock, induction of labour, caesarean section, transfer to ICU, readmission to hospital within 3 months and maternal death. In particular, Vigod et al. [72] single out maternal death, as despite being a very rare outcome overall, this remains five times more likely for women with schizophrenia (adjusted odds ratio 5.64, CI 1.39–23.0). However, in the same authors' 2015 [39] re-examination of the same patient group, comparison with matched cohorts did not show any of these elevated risks in the treatment group, aside from labour induction and operative vaginal delivery.

Matevosyan [24] took a highly structured approach to the analysis of risk conferred by the diagnosis of schizophrenia, pooling data from multiple studies to arrive at odds ratios of various outcomes for pregnant women with schizophrenia. This author found that these women were not at statistically greater risk of induction of labour or emergency caesarean section than their peers.

Women with bipolar disorder were much more likely to have instrumental deliveries than their peers, especially those who were treated with medication (aOR = 1.39, 1.09–1.79) [1, 2]. Those treated were also much more likely to have caesarean section delivery (aOR 1.56 (1.20–2.03)) or to be induced (aOR = 2.12, 1.68–2.67).

7.8.1 Caesarean Section Delivery in Women Taking Antipsychotics in Pregnancy

Diav-Citrin et al. [84] found that women treated with haloperidol were more likely to have caesarean deliveries (25.5% vs. 16.3%, $p = 0.014$).

Sadowski et al. [26] found a higher rate of planned caesarean section, at 11.5% in women exposed to second-generation antipsychotics in pregnancy, compared with 2.6% in those unexposed. Reis and Kallen's [20] treatment cohort also had a significantly higher rate of caesarean section than those not taking antipsychotic medication for a mental health indication, or not taking medication at all. This study also found an increased risk of placental abruption and induction of labour in women treated for mental health problems, but neither of these outcomes reached significance.

Kulkarni et al. [4] examined 147 women taking typical and atypical antipsychotics in pregnancy for psychotic and mood disorders. This group demonstrated high rates of caesarean section at 40%, compared with the expected population rate of 31.5%.

Interestingly, Petersen et al. [36] found that rates of caesarean section were higher in women who took antipsychotic medication in pregnancy than those who had never been exposed to this but that the significance of this difference disappeared when adjusting for health and lifestyle factors. High rates of caesarean section were seen in women taking both typical (26.8%) and atypical (24.6%) antipsychotics in pregnancy, compared with the general population cohort (18%).

7.9 Congenital Malformations and Antipsychotic Medications

Rates of congenital malformation found in babies of women taking antipsychotic medications are only meaningful when compared with accurate rates for the general population. Over time, reported rates for congenital malformations in the general population have varied widely in different settings around the world, from 2.0 to 5.5 [85]. A recent survey of 20% of the American population suggests that the rate of congenital malformations in this ethnically and socioeconomically diverse nation is 28.9/1000 [86]. The authors note this to be a conservative estimate as it excludes stillbirth and terminations.

Additionally, a distinction should be drawn between major malformations, with implications for survival or lifelong illness, and minor malformations, which may be mild cosmetic defects that are easily correctable. Some investigators make this distinction and others do not.

There is a broad range of data available on congenital malformations. That which applies to first-generation antipsychotics often borrows from the use of phenothiazines over the past 40+ years for nausea in pregnancy. The use of this data could be considered problematic, as it isn't assessing women treated for major mental illnesses, and doses are typically small and intermittent. Hence these data sets probably don't really examine the true risks for the population of women with major mental illnesses, whether bipolar disorder or schizophrenia. However, some authors have defended this practice, arguing that it eliminates confounding for indication; that if schizophrenia itself confers an increased risk of malformations, then using data from women who don't have this diagnosis will eliminate this confounder.

7.9.1 Managing Confounding by Indication: What Is the Risk of Congenital Malformations Associated with Underlying Mental Illness in Pregnancy?

Reis and Kallen [20] found an increase in the rates of congenital malformations in women taking antipsychotic medication for their mental health, compared with women taking antipsychotic medication for hyperemesis. When these numbers

were adjusted to consider only major malformations, this difference became statistically significant. These authors excluded preauricular tags, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testis, unstable hip and naevus. These authors also excluded babies with chromosomal abnormalities.

In common with other authors, Reis and Kallen [20] found that women taking antipsychotics for mental illness were significantly less likely than their peers to take multivitamins, folate or thyroid hormone but much more likely to take other psychotropics, including anticonvulsants, benzodiazepines, sedatives, hypnotics and antidepressants of all types.

Other authors take a different approach to confounding by indication. Petersen et al. [36] examined data from general practice databases in the UK, comparing three groups of women: those who had taken antipsychotics prior to pregnancy but ceased, those who took antipsychotics throughout pregnancy and those who had never been exposed to antipsychotic medication. In this study, 3.4% of women taking antipsychotics throughout pregnancy (416 women) had babies with major congenital malformations, in comparison with 2.2% of women taking antipsychotics prior to, but not during pregnancy (670 women), and 2.1% of those women not exposed to antipsychotics (the reference cohort of 319,520). The difference between these cohorts was not statistically significant (adjusted risk ratio = 1.59 with 95% CI 0.84–3.00). This was a compelling study as it attempted to distinguish the risk associated with diagnosis from the risk associated with medication treatment in pregnancy. However, this may only have eliminated the risk for women with illnesses that were not severe enough to require medication treatment throughout pregnancy. If these less unwell women were at lesser risk of congenital malformations, this study might have missed this distinction.

7.9.2 Schizophrenia and the Risk of Congenital Malformations: Specifically Cardiovascular Risk

Jablensky et al. [15] provided one of the earlier large-scale population-based data sets from which to examine low-incidence events such as congenital malformations. For that reason, and for its rigour of analysis, this was a seminal paper. The drawback of this approach was that medication and other treatment for the individual, as well as other data affecting risk of teratogenesis, were not available. These authors found no significant increase in overall birth defects in women with schizophrenia compared with the reference group, though there was a trend (6.0% vs. 4.9%). When examining specific defects, however, this study found a significant increase in cardiovascular anomalies, including atrial and ventricular septal defects, patent ductus arteriosus and aortic anomalies (adjusted odds ratio 2.50), in babies of women with schizophrenia, as well as a significant increase in minor physical abnormalities. Jablensky singles out patent ductus arteriosus, with a tenfold increase in incidence in babies of women with schizophrenia, ventricular septal defect (with a threefold increase in risk) and atrial septal defect, with a doubling of risk.

These authors suggest that all of these abnormalities have a strong genetic component and hypothesise a mechanism: patent ductus arteriosus linked to abnormal expression of the prostaglandin receptor, an abnormality also found in people with schizophrenia and their relatives; ventricular septal defect linked to velocardifacial syndrome, which in turn confers a higher risk for schizophrenia; and atrial septal defect linked to chromosome 6p21.3 deletion, also related to schizophrenia risk. Vigod et al. [72] found an increased risk for congenital anomalies (adjusted odds ratio of 1.94 with CI 1.56–2.41) for babies of women with schizophrenia, but did not include information on treatment modality. Pooling data on risk relating to a diagnosis of schizophrenia, Matevosyan [24] found that rates of congenital defects were significantly higher in babies of mothers with schizophrenia (RR 2.1, CI 1.1–3.8), though these defects were not further characterised in this study. Hizkiyahu et al. [28] found a significantly higher rate of congenital malformations in a cohort of women with schizophrenia than their comparators: 11.3% vs. 5.2%. Both of these rates are so high that they suggest that minor as well as major malformations may have been considered as part of this study.

7.9.3 Bipolar Disorder and the Risk of Congenital Malformations

Specifically examining women with bipolar disorder, Boden et al. [1, 2] did look at congenital malformations in patients taking antipsychotic medications, though did not further stratify these patients into medication class. These authors found a malformation rate of 3.5% in this group, with p of 0.11, one each of talipes equinovarus, cleft palate, urinary system agenesis and heart malformation.

7.9.4 Typical Antipsychotic Medication and the Risk of Congenital Malformations

The most recent large-scale study of typical antipsychotics [84] was an international collaboration which followed 188 women prescribed with haloperidol at therapeutic doses for major mental illness (median 5 mg/day) throughout pregnancy, including in the first trimester in 78.2% of women. Most of these women, as in other studies, were also taking other medication (75%). These women were also, as in other studies, more likely to be older and to smoke than the reference group. This study found no statistical increase in the rate of major malformations in the group treated with haloperidol.

Munk et al. [87] found increased rates of congenital abnormalities which did not reach significance in a small cohort of 69 babies exposed to first-generation antipsychotics when compared with the general population in several Danish counties.

7.9.5 Typical vs. Atypical Antipsychotic Medication: Is There a Difference in Risk?

7.9.5.1 Voluntary Reporting Cohorts and Case Control Studies of Congenital Abnormalities in Babies Exposed to Atypical Antipsychotics In Utero

I note the retrospective study by Wichman [88] of 16 babies exposed in utero to atypical antipsychotics, compared with a tertiary hospital peer cohort. The rate of malformations was 6.25% (one baby) in this (very low-powered) study, with three babies exhibiting heart murmurs which resolved by the end of the first year.

Brunner et al. [85] found a congenital malformation rate of 4.4% in 610 pregnancies using voluntary reporting to Eli Lilly of pregnancy outcomes for women exposed to olanzapine. The authors suggest that the general population rate of malformations is 3–5%, and hence 4.4% falls within the expected reference range, consistent with most international surveillance authorities [89].

McKenna et al. [3] provide an earlier but well-conducted study of rates of congenital malformations amongst babies exposed to atypical antipsychotics in pregnancy, comparing exposed women with unexposed age-matched peers. They found that the exposed group was overall more likely to have high rates of factors known to worsen the outcome of pregnancy, including having an unplanned pregnancy (57% vs. 23%) and not taking folate or multivitamins during pregnancy (15% vs. 2%). Interestingly, both groups reported relatively high rates of alcohol use in pregnancy (14% vs. 12%), but there was a significant difference in smoking rates (38% vs. 13%). This study, as most others, reported a high rate of polypharmacy in women taking psychotropics, with 57% also taking an antidepressant, 34% a benzodiazepine and 17% an anticonvulsant (of whom 72% were taking valproate). These authors found a rate of major malformations in babies exposed to atypical antipsychotics of 0.9% vs. 1.5%, both lower than that found in most general population samples.

Cohen et al. [90] at the Massachusetts General Hospital reported on results from the National Pregnancy Registry for Atypical Antipsychotics at the Massachusetts General Hospital, similar to the NRAMP study in Australasia, to track outcomes for women taking second-generation antipsychotic medication in pregnancy. This group published data on 214 babies exposed in pregnancy and found there was no significant increase in risk in the exposed group (1.4%, CI 0.29–4.04). Unadjusted odds ratio found an increase in rates of 1.25 in exposed babies over those unexposed. However, after performing sensitivity analysis, these authors used propensity scoring to assess for the relative contribution of confounders they considered, using the diagnosis of bipolar disorder as a basis for comparison. Confounders considered included smoking, stimulant, illicit drug or alcohol use in the first trimester, concomitant anticonvulsant, lithium, anxiolytic, sedative, antidepressant, or typical antipsychotic use, a diagnosis of depression or anxiety, chronicity of illness, the use of prenatal vitamins, ethnicity, age, BMI or planned pregnancy. Incorporating these factors reduced the adjusted odds ratio to close to parity. However, excluding women taking known teratogens including valproate, lithium, isotretinoin and illicit drugs, the odds ratio returned to 1.25.

7.9.5.2 Large-Scale Studies Examining Rates of Congenital Abnormalities in Women Taking Atypical Antipsychotics

Habermann et al. [21] found a statistical difference between the rates of congenital abnormalities in babies of women taking second-generation antipsychotics and those unexposed (OR 2.13, 95% CI 1.19–3.83), though not between babies of those taking first-generation antipsychotics and those unexposed (OR 1.75, 95% CI 0.80–3.80). This group adjusted carefully for known confounders, including maternal age, alcohol consumption, smoking, BMI, past history of malformations in pregnancy and past history of miscarriage. Of these, only alcohol had a significant influence on the outcome and was therefore included in the final analysis. The difference in incidence remained significant after this adjustment. No specific second-generation antipsychotic was associated with statistically significant differences in rates, though these rates did vary; a rate of 3.59% was found with quetiapine (5/139) and 6.81% (3/44) with aripiprazole. No malformations were observed with amisulpride (though low numbers were examined, 13) or zotepine (2).

Habermann et al. [21] drew a distinction between major and minor malformations, and though these authors found a slightly higher rate of minor malformations in the group of women taking first-generation antipsychotics (5.5%) than those taking second-generation antipsychotics (3.2%), this difference was not significant.

Huybrechts et al. [34] recently published a large-scale data set examining 1.3 million pregnancies, of whom 9258 took an atypical antipsychotic in the first trimester and 733 took a typical antipsychotic during the same period. In common with other researchers [4, 21], the most commonly used atypical antipsychotic medication was quetiapine (46% of all atypical prescriptions). These authors observed that, as in other studies, women who took antipsychotic medication in pregnancy were generally older and in poorer health and used more other medications and illicit drugs known to be associated with congenital defects than their peers. Therefore, these researchers controlled for indication and other confounders including smoking, ethnicity, age, obesity and general physical and obstetric morbidity. Considering the large numbers of factors controlled for, this study used propensity scores as a fairly novel method of data reduction. Absolute rate of congenital defects for those treated with atypical antipsychotics was higher at 4.5% (95% CI 4.05–4.89) than for those treated with typical antipsychotics at 3.8% (95% CI 2.66–5.47) or the baseline rate in the general population in this study of 3.3%.

Overall unadjusted cardiac risks were greater for babies of all women taking antipsychotic medications but disappeared for those taking typical antipsychotic medications when psychiatric illness was accounted for. Huybrechts et al. [34] noted that a large component of the increased risk for both overall and cardiovascular anomalies in babies exposed to atypical antipsychotics was accounted for by risperidone.

Consistent with the outcomes for Huybrecht's group, Montastruc et al. [91] have noted in a recent very large-scale study examining all outcomes from the World Health Organization Collaborating Centre for International Drug Monitoring over four decades that only two second-generation antipsychotic medications showed a signal of increased risk of congenital malformations: risperidone and aripiprazole,

specifically in relation to gastrointestinal malformations. This is a surprising finding, as major gastrointestinal abnormalities (oesophageal atresia, anorectal atresia; some authors include in this list cleft lip and palate) are not commonly noted in the literature to date in relation to novel antipsychotics. This group also found a signal for phenothiazine medications with a piperazine side chain. However, the widespread use of these medications for nausea in pregnancy throughout the past 60 years might influence the utility of this finding in relation to antipsychotic medications specifically used for mental illness. By contrast, risperidone and aripiprazole are very rarely prescribed for nausea in pregnancy. The authors were cautious not to attribute causality to this finding but did note the necessity for further research on medication-specific risks of teratogenicity, echoing other authors such as Gentile [16]. Considering the possibility that specific medications could confer specific risks, it is worthwhile examining some of these medications in more detail.

7.9.5.3 Retrospective Reviews of Data Reporting Congenital Abnormalities

Einarsson and Boskovic [92], of the Motherisk team at the Hospital for Sick Children in Toronto, performed a retrospective review of all studies relating to typical and atypical antipsychotics at that time. These authors discussed phenothiazines including promethazine, widely used for nausea in pregnancy, and noted that these medications do not seem to be associated with any known adverse outcomes for babies. Prochlorperazine, also widely used for nausea, was used in the first trimester in 877 pregnancies and did not result in an increase in the rate of congenital abnormalities [93]. Similarly, Briggs et al. [94] found no increase in risk above baseline in 704 babies after first trimester exposure to prochlorperazine. These researchers found a study in 1982 which evaluated 264 women taking chlorpromazine in pregnancy for nausea, with no increase in the rate of malformations amongst their babies [95]. Einarsson cites Diav-Citrin et al. [84] in relation to haloperidol with no increased risk found and Slone et al. [93] in relation to perphenazine (no increased risk found in relation to perinatal mortality, birth weight or intelligence at 4 years). Trifluoperazine, now rarely used in most centres, was evaluated in relation to risk of exposure in early pregnancy in a study of 480 women, for whom the incidence of birth defects was 1.1%; well within the expected incidence of the general population [96]. For completeness's sake, Einarsson and Boskovic [92] include data on loxapine (three cases of abnormalities including achondroplasia, unspecified malformations and tremors at 15 weeks old [97]) and thioridazine (two major malformations in 63 exposed newborns [94]). Einarsson reports extremely limited data on flupenthixol (three pregnancies reported without abnormalities) and fluphenazine [94].

Though these authors did not further discuss the results, they mentioned that post-marketing data for clozapine included 523 cases of known exposure to clozapine in pregnancy, which resulted in 22 reports of malformations without any pattern of defects found. Similarly, correspondence with the manufacturers by the authors resulted in a report of 144 prospective and 98 retrospective pregnancy outcomes for women taking olanzapine with no increase in rates of malformations but no further

information regarding these. Discussion with the manufacturer of quetiapine by the authors resulted in 298 pregnancy exposures, of which there were 14 reports of congenital anomalies with no pattern of defects found. Discussion with manufacturers of ziprasidone by the authors revealed 57 known pregnancy outcomes, of which 50 showed no malformation, five had miscarriages, one twin pair of which one of the twins had a malformation and one woman had a stillbirth. The frustrating aspect of these relatively large data samples is the paucity of further information on women and their babies in every category, limiting their utility for ascertaining risk.

Gentile [16] painstakingly collated all available data, including case reports, on both typical and atypical antipsychotics at time of writing, and found inadequate human data to guide prescribing on amisulpride, ziprasidone and sertindole. He found three case reports on aripiprazole. Hence he advised avoidance of all these medications in pregnancy due to limited data. He found 200 babies exposed to clozapine in utero, of whom there were 15 cases of congenital malformation reported, though these could not be further investigated in most cases. He found 419 cases of olanzapine-exposed foetuses, of whom 26 had congenital malformations, including neural tube defects in four. Further, this study found 227 babies exposed to quetiapine, of whom eight had congenital malformations, not further specified, and 321 babies exposed to risperidone, of whom 15 had congenital malformations. Four hundred eleven babies were exposed to haloperidol in utero, of whom 14 cases of foetal abnormalities were observed, including three limb malformations. Gentile notes the risks of late uterine exposure associated with haloperidol, including body temperature instability. He also found over 400 cases of exposure to chlorpromazine, of which only five cases of malformations were described. His recommendations based on this review are discussed elsewhere.

7.9.5.4 Meta-analyses of Data Reporting Congenital Abnormalities

Coughlin et al. [98] attempted to provide a comprehensive analysis of available data, given the small sample sizes of most studies. This meta-analysis compiled results from 3346 babies over a variety of outcomes. Investigators noted a large degree of heterogeneity amongst trials, but no publication bias. This study found no significant difference between the rates of congenital malformations for babies exposed to either typical or atypical antipsychotics. The most common abnormality reported was a heart defect. This meta-analysis found that exposure to antipsychotic medication, typical or atypical, significantly increased the risk of heart defects with OR 2.09, CI 1.50–2.91, $p < 0.001$.

A similar approach to aggregating data was undertaken by Terrana et al. [99], focusing on outcomes for babies of mothers taking second-generation antipsychotics in pregnancy, specifically congenital malformations. Examining all reported case control studies, this group found an aggregate of 12 studies meeting at least level 6 on the Newcastle-Ottawa assessment scale. A total of 1872 subjects formed the final pool of data including 631 women taking olanzapine, 424 taking quetiapine, 314 taking risperidone, 254 taking aripiprazole, 152 taking clozapine, 37 taking ziprasidone, 17 taking amisulpride and seven taking zotepine. Importantly, when

this data was analysed, babies of these women were significantly more likely to have congenital malformations, with OR 2.03 (1.41–2.93). A specific pattern of malformations was not found.

7.9.6 Polypharmacy: Does the Use of Multiple Medications in Pregnancy Escalate the Risk of Congenital Malformations?

Examining data from the Motherisk Program in Toronto, Sadowski et al. [26] found that rates of major congenital malformations were higher in the cohort exposed to second-generation antipsychotics than the unexposed group, at 6.2% compared with 2.6%. However, this difference did not reach significance. All babies who had major malformations at birth were exposed to polypharmacy in utero, suggesting that there may be other factors at play in the development of congenital malformations in this group. These authors suggested that the practice of polypharmacy severely affected outcomes for babies and advocated for the use of a minimal number of medications in pregnancy.

7.9.7 Cardiovascular Risk Revisited: The Risk Posed by Specific Classes of Antipsychotic

When considering major malformations, the striking example in the study by Habermann's group was cardiac malformations. At a rate of 2.8% in the second-generation-exposed subgroup in comparison with 1.4% in the first-generation-exposed and 0.6% in the unexposed subgroup, these authors found a significant difference between the second-generation-exposed and unexposed cohorts (OR = 3.21, 95% CI 1.34–7.67). These defects were largely atrial or ventricular septal defects. This result is complicated by the co-administration of lithium to three children in the second-generation-exposed cohort (the total number of children with a cardiovascular abnormality in this cohort was 12).

In reference to the finding of elevated rates of cardiac malformations in babies of women taking second-generation antipsychotics in pregnancy, Habermann et al. [21] recommends that babies of mothers exposed to these medications in the first trimester of pregnancy should be offered a detailed ultrasound to confirm normal cardiac development.

7.9.8 Special Cases

7.9.8.1 Risperidone

Coppola et al. [100] found 197 retrospective reports of risperidone in pregnancy, amongst which there were 12 reports of major congenital abnormalities without any clear pattern of organ system involvement. Ten of these women were also taking

other medications known to increase the risk of congenital abnormality. These authors concluded that the low rate of malformations reported (6.09%), together with the absence of specific organ pattern involvement, suggesting that risperidone is not likely to be implicated in specific teratogenic risk.

In their large data set analysis, Huybrechts et al. [34] found that within the group of women taking atypical antipsychotic medication, the overall risk of malformations in those taking risperidone was significant (RR 1.26, 95% CI 1.02–1.56) and remained appreciable, though non-significant when considering cardiac defects specifically (RR 1.26, 95% CI 0.88–1.81). Interestingly, this group also examined the relationship between dose of medications and the risk of defects. This did not appear to be a factor for any medications aside from risperidone, for which doses above 2 mg/day were related to an increased risk for cardiac malformations (RR 2.08, 95% CI 1.32–3.28). These authors are cautious about interpretation of their results, referring to the increased risk associated with risperidone use in the first trimester as a "safety signal", though they also point to a prior systematic review [101] which found a similar unadjusted RR of 1.5 for risperidone and major malformations (though 95% CI was 0.9–2.2).

7.9.8.2 Aripiprazole

Aripiprazole is an unusual antipsychotic with a distinct mode of action, acting as a partial agonist at D2 and 5-HT1A receptors and as an antagonist at 5-HT2A receptors [73]. Its use merits specific discussion because of its uniqueness in mode of action (which could lead to unique teratogenic risks) and its reduced effect on weight gain when compared to other second-generation antipsychotic medications such as olanzapine or quetiapine. Hence it may be an option considered if weight gain, gestational diabetes, hypertension or other metabolic risks are a major concern for a woman considering pregnancy.

A recent review conducted by Cuomo et al. [102] suggests that concerns raised by non-human teratogenesis relating to aripiprazole use have not been replicated in human subjects. These researchers not only mention the miscarriage signal in aripiprazole use in pregnancy reported by Sakai et al. [103] but also mention other studies which do not seem to support an increase in the rate of congenital malformations or of miscarriage [21, 34].

Bellet et al. [73] divided congenital malformations into major and minor categories according to EUROCAT and found that the rate of major malformations was higher in the group exposed to aripiprazole (2.8%) compared with the unexposed group (1.2%), though this difference was not statistically significant. Interestingly, one of the babies suffering a malformation had a gastrointestinal tract abnormality (oesophageal atresia) consistent with the findings by Montastruc et al. [91] in regard to aripiprazole in pregnancy (see previous section for more detail).

7.9.8.3 Clozapine

The use of clozapine in pregnancy presents special challenges. Most women take clozapine for treatment-refractory symptoms of psychosis, hence

switching medications or ceasing medications during pregnancy is not always feasible. Cessation of clozapine in particular can result in severe relapses of psychotic symptoms, as demonstrated by case reports [104]. The chaos associated with a severe relapse of psychosis could have multiple negative effects for both mother and baby. Therefore, decisions about treatment with clozapine in pregnancy need to be well informed of all potential risks to both the mother and baby.

Mehta and Van Lieshout [76] note that Novartis Pharmaceuticals has reported 523 cases of clozapine exposure in pregnancy, of whom 22 have reported malformations. At 4.2%, this lies within baseline rates for the general population. Higher rates of 8.2% have been reported by Dev and Krupp [105] in a series of 61 babies exposed to clozapine. Boden et al. [1, 2] reports macrocephaly associated with clozapine or olanzapine in pregnancy. Kulkarni et al. [4] report on the relatively high rate of congenital abnormalities in their group of babies exposed to clozapine in utero: of 11 babies, two were born with major congenital abnormalities—craniosynostosis, hypospadias and hypertelorism in one baby and gastroschisis and horseshoe kidney in the other. Notably, there does not appear to be a pattern of organs affected by clozapine in this case series.

7.10 Elective Terminations, Spontaneous Abortion, Miscarriage and Stillbirth

Many authors have commented on the high rate of elective terminations found in women prescribed with antipsychotics in pregnancy [3, 21, 34, 84, 85, 98]. Several have speculated on the reasons for this, some citing the high rates of unplanned pregnancy in this group [3].

A 2015 meta-analysis by Coughlin et al. [98] confirmed this trend, with pooled odds ratio of 5.98 (CI = 2.94–12.14, $p < 0.001$). These authors considered the possibility that this high rate may be masking a concealed higher rate of congenital malformations but noted that the indication for termination was not mentioned in the studies which reported this result. Huybrechts et al. [34] noted that the relative risk for any congenital malformation in the context of atypical antipsychotic use increased from 1.05 to 1.09–1.14 after accounting for the increased rates of termination amongst treated and untreated women.

These increased termination rates appear to relate to women taking both typical and atypical medications. Diav-Citrin et al. [84] found a higher rate of elective terminations in women exposed to haloperidol than a control group (8.8% vs. 3.8%), $p = 0.004$. Habermann et al. [21] found an increased rate of elective terminations of pregnancy in women taking both second-generation and first-generation antipsychotics (9.4%, 8.1%) compared with those not taking these medications (5.7%). McKenna et al. [3] found a high rate of elective terminations amongst women exposed to atypical antipsychotics: 9.9% vs. 1.3% in the comparator group.

7.10.1 Stillbirths and Neonatal Deaths in Women with Major Mental Illness

Lee and Lin [47] cite Howard et al. [13, 106] in suggesting that women with a history of psychotic disorders have higher rates of stillbirths and neonatal deaths than other women. These authors also cite other earlier studies suggesting that women with schizophrenia are at increased risk of stillbirth [22, 31, 107, 108] and cite Webb et al. [109] in suggesting that maternal mood disorders are associated with a higher risk of fatal congenital defects.

Whereas these earlier studies seemed to correlate a diagnosis of major mental illness with an increased risk of stillbirth, this finding is not corroborated by more recent research. Habermann et al. [21], Vigod et al. [39], Reis and Kallen [20], Diav-Citrin et al. [84], Terrana et al. [99], Coughlin et al. [98], Brunner et al. [85] and Boden et al. [1, 2] all found rates of stillbirth or neonatal death which approximated rates found in the general population. Jablensky et al. [15] found no significant differences between women with schizophrenia, affective psychosis or the general population in terms of stillbirth, neonatal deaths or deaths within the first year of life. Of note, Vigod et al. [72] did not find a significantly elevated risk of neonatal death in a population-based sample examining obstetric outcomes for women with schizophrenia. However, in their subsequent review of research findings, the authors commented that the observed neonatal mortality rate of 1% was still twice that of the general population.

7.10.2 Miscarriage/Spontaneous Abortion/Ectopic Pregnancy/ Foetal Death In Utero

In a pooled meta-analysis of women diagnosed with schizophrenia, Matevosyan [24] found rates of miscarriage of 5.1% (RR = 2.04). The authors reported this to be a higher rate than the reference population, though this difference did not reach significance. Sadowski et al. [26] defined miscarriage as occurring prior to 20 weeks and foetal death as occurring after 20 weeks and found that neither occurred more frequently in women exposed to second-generation antipsychotics. Habermann et al. [21] found no significant increase in risk of spontaneous abortion after exposure to antipsychotics either second or first generation, reporting consistency with outcomes observed by other authors [110–112]. Diav-Citrin et al. [84], Terrana et al. [99], Coppola et al. [100], Coughlin et al. [98] and Brunner et al. [85] found no significant difference between rates of miscarriage in women treated with either typical or atypical antipsychotic medications and the general population. Two authors mentioned no difference in rates of ectopic pregnancy between women treated with antipsychotics and those unexposed [84, 85].

7.10.3 Specific Antipsychotics: Aripiprazole and the Risk of Miscarriage

Sakai et al. [103] examined the relative risk for miscarriage of aripiprazole specifically, in comparison with other second-generation antipsychotics including risperidone, olanzapine and quetiapine. These researchers used a voluntary reporting database in Japan for this study. The relative risk for spontaneous miscarriage was found to be significantly greater for women taking aripiprazole than for unexposed women; this significant difference was not present for the other second-generation antipsychotics: ROR 2.76 (CI 1.62–4.69). Of the 18 women reporting miscarriage with aripiprazole, 12 had a diagnosis of schizophrenia, treated with a median dose of aripiprazole 12 mg. This finding has been discussed elsewhere in the literature; Cuomo et al. [102] not only mention the miscarriage signal for aripiprazole use in pregnancy reported by these Japanese researchers but also mention other studies which do not support an increase in the rate of congenital malformations or of miscarriage for women taking aripiprazole [21, 34].

By contrast with research by Sakai et al. [103], Bellet et al. [73] conducted a review of 86 cases of babies exposed to aripiprazole in pregnancy excluding all exposures to known teratogens, including other psychotropic medications, in the first trimester. This team drew cases from a reporting service available in France for monitoring adverse outcomes and screened for substance use, smoking and other lifestyle factors in the women identified. Women with pre-existing diabetes were excluded. Pregnancy outcomes included a high rate of elective termination (9.3%), consistent with other studies, and a miscarriage rate within the general population rate (again, 9.3%).

7.10.4 Clozapine and the Risk of Stillbirth or Miscarriage in Pregnancy

Mendhekar et al. [104] report on a stillbirth associated with monotherapy of clozapine 75 mg throughout pregnancy, including the first trimester. Aside from case reports, there is very little information about stillbirth, miscarriage or ectopic pregnancy rates in babies exposed to clozapine in pregnancy.

7.11 Premature Infants/Low-Birth-Weight Infants

7.11.1 Schizophrenia and Premature Birth/Low Birth Weight: Another Instance of Potential Confounding by Indication

Looking primarily at diagnosis rather than treatment modality and examining women treated prior to the era of widespread use of atypical antipsychotics, Jablensky et al. [15] noted a slight trend to preterm birth, a lower mean birth weight,

reduced head circumference and reduced length in babies of women with schizophrenia. There was a suggestion in this study that babies of women with schizophrenia experienced intrauterine growth restriction after adjustment for ethnicity, maternal age, infant gender, plural birth and marital status. This group also adjusted for the expected impact of smoking (extrapolated from other studies; this data set did not include smoking rates) and found an additional residual effect of schizophrenia diagnosis alone (or the presence of an unaccounted-for additional moderator). This study could be considered a proxy for examining treatment using first-generation antipsychotic agents, as it studied a population of women diagnosed (and presumably treated) in the 1980s.

Consistent with these earlier results, Vigod et al. [72] found a much higher rate of preterm birth in the babies of women with schizophrenia regardless of treatment modality, with rates of 11.2% compared with 6.2% in the control group. Adjusted odds ratio was 1.75 (CI 1.46–2.08). Women with schizophrenia were also statistically more likely to deliver very preterm infants (<32 weeks). Similarly, the women in Reis and Kallen's 2008 [20] cohort taking antipsychotics for mental health reasons were significantly more likely to have babies born before 37 weeks, with an odds ratio of 1.73 (95% CI 1.31–2.29). Matevosyan [24] found rates of premature labour in women with schizophrenia which the author considered high (5.1% RR 1.98) but which remained well within statistical norms. This author did find a statistical increase in rates of babies with growth retardation born to mothers with schizophrenia (RR 2.16, CI 1.48–3.87). These findings were echoed by Hizkiyahu et al. [28], who found that babies born to women with a diagnosis of schizophrenia were significantly more likely to be of low birth weight (13.4% vs. 7.8%, $p = 0.042$).

7.11.2 Women with Schizophrenia and Low-Birth-Weight Babies Born at Term

Vigod et al. [72] found a correlation between diagnosis of schizophrenia in the mother and small-for-gestational-age infants, though these researchers did not stratify according to treatment. The unadjusted odds ratio for small-for-gestational-age babies (<3rd centile) born to women with schizophrenia was 1.56 (95% CI 1.25–1.95). Reis and Kallen [20] found that women taking antipsychotics for mental health reasons were also significantly more likely to have babies born at low birth weight (<2500 g): OR 1.67 (95% CI 1.21–2.29). Jablensky et al. [15] found a significant increase in low-birth-weight infants born to mothers with schizophrenia, regardless of the timing of onset of their illness (whether prior to or after the birth). This approach seemed to account well for any effect associated with treatment.

Lin et al. [37] found that women with diagnoses of bipolar disorder and schizophrenia were more likely than women without a mental illness to have babies of low birth weight, even after adjustment for sociodemographic and metabolic factors. These babies were also more likely to be small for gestational age.

7.11.3 Bipolar Disorder and Premature Birth/Low-Birth-Weight Infants

Lin et al. [37] found that women with bipolar disorder were more likely than relatively demographically matched controls to have preterm babies (OR 2.08 CI 1.53–2.83). In support of this view, Lee and Lin [47] cite MacCabe et al. [38] in suggesting that mothers with mood disorders have elevated risk of preterm birth and small-for-gestational-age babies. Both treated and untreated women with bipolar disorder studied by Boden et al. [1, 2] had similarly increased rates of preterm birth, further supporting the view that perhaps this risk may not relate to medication treatment but instead to other factors underlying the diagnosis or associated sociodemographic risks.

7.11.4 Women with Bipolar Disorder and Low-Birth-Weight Babies Born at Term

In the 2012 study by Boden et al. [1, 2], women with bipolar disorder who remained untreated were much more likely to have babies of low birth weight at delivery. Interestingly, this study examined head circumference, which alone of weight, length and head circumference remained significant after adjustment for confounders in women with untreated bipolar disorder. These researchers suggested that maternal psychosocial stress in pregnancy in the context of untreated bipolar disorder may be the mechanism responsible or that women with bipolar disorder were more vulnerable to adverse neonatal outcomes such as low birth weight because of associated demographic and lifestyle factors. These researchers also drew an association between small-for-gestational-age infants and neonatal hypoglycaemia, which could be associated primarily with the condition of small for gestational age itself rather than with the administration of psychotropic medications.

7.11.5 Typical Antipsychotic Medications and Prematurity/Low Birth Weight

There appears to be a consensus relating to the correlation between typical antipsychotic exposure and preterm birth in most early studies, and this is borne out in recent work as well. The study by Munk et al. [87] suffered from low numbers in the target population but did find a trend towards risk of preterm birth and low birth weight in women taking first-generation antipsychotics throughout pregnancy.

Diav-Citrin et al. [84] found that gestational age at delivery was lower in a cohort of women taking haloperidol for multiple different diagnostic indications, as was median birth weight. Babies exposed to haloperidol in pregnancy were two times more likely to be born prior to 37 weeks. When the data were analysed for the relative strength of predictors of low birth weight, only haloperidol and smoking were significant predictors.

7.11.6 Typical Antipsychotic Medications and Low-Birth-Weight Babies Born at Term

Habermann et al. [21] found that babies of women taking first-generation antipsychotics had the lowest birth weights when compared with babies of women taking second-generation antipsychotics or those unexposed but that the difference in birth weights was not clinically significant, especially when preterm babies were excluded from this analysis: these researchers found median weight at delivery of 3.38 kg for first-generation-exposed babies compared with 3.4 kg for second-generation-exposed babies and 3.44 kg for unexposed babies. Diav-Citrin et al. [84] noted that their group of term infants exposed to haloperidol in utero was lighter by 165 g than the reference cohort. Overall, Newham et al. [25] found in a small sample that babies exposed to typical antipsychotics weighed significantly less than babies exposed to atypical antipsychotics and then a reference group of unexposed babies ($p < 0.05$).

7.11.7 Atypical Antipsychotics and Prematurity/Low Birth Weight

Infants exposed to second-generation antipsychotics in the study by Sadowski et al. [26] were approximately 2.5 times more vulnerable to prematurity compared with controls (10.6% vs. 4.3%). There was also a marked difference between gestational age of neonates exposed to one second-generation antipsychotic in comparison with those exposed to polypharmacy ($p = 0.005$). Similarly, unmatched cohorts in the study by Vigod et al. [39] showed a higher rate of preterm birth in women taking atypical antipsychotic medication in pregnancy, at 14.8% vs. 10.3%. However, there was not a significant increase in low birth weight even in the unmatched cohort in this study. Boden's group of women taking only antipsychotic medication demonstrated higher rates of preterm birth when comparing medications other than olanzapine and clozapine with unexposed groups. McKenna et al. [3] found a trend to prematurity in women treated with atypical antipsychotics (13% vs. unexposed 8%), but this difference was not significant. 10% of exposed babies were of low birth weight vs. 2% of comparators; this difference was significant ($p = 0.05$).

Wichman [88], conducting a retrospective review of birthing records for a tertiary referral maternity centre, found 16 women prescribed with atypical antipsychotics in pregnancy. These women predominantly had diagnoses of major depressive disorder (44%), schizoaffective disorder or bipolar disorder, and over half were prescribed quetiapine. There is no data on concomitant medications, which are likely to have been prescribed given the diagnostic categories treated. The average age at delivery was 37 weeks and 5 days, with 18.75% of babies born prematurely. Comparison data were not available in this study to evaluate significance. Average birth weight was low, at 3188 g.

Terrana et al. [99] conducted a meta-analysis of cohort studies examining second-generation antipsychotics. This group found that these babies were significantly more at risk of preterm birth (OR = 1.85 (1.20–2.86)), though this

impact was decreased under a fixed effects model (OR = 1.51, CI 1.15–1.98) and further decreased with adjustment (aOR = 1.34, CI 0.85–2.11) to lose statistical significance. This meta-analysis did not find a significant increase in the risk for small-for-gestational-age or large-for-gestational-age babies, respectively, though noting that the studies evaluating large-for-gestational-age babies were not homogeneous.

Hence the data is more mixed in relation to the risk of low birth weight in babies exposed to atypical antipsychotics in pregnancy, though the trend to mild prematurity seems in most studies to remain.

7.11.8 Atypical Antipsychotics and Low-Birth-Weight Babies Born at Term

Sadowski et al. [26] did not find a significant difference in the incidence of babies who were small for gestational age at delivery between women exposed to second-generation antipsychotics and those unexposed. This group also did not find any significant difference in birth weight. Examining antipsychotic medication exposure in pregnancy, Boden et al. [1, 2] found a much higher unadjusted risk (more than double) of small-for-gestational-age babies than the general population, regardless of the type of antipsychotic medication to which they were exposed. However, significance disappeared once maternal factors were adjusted for. McKenna et al. [3] found 10% of exposed babies had a low birth weight, compared with 2% of unexposed babies. This difference was not statistically significant.

A meta-analysis by Coughlin et al. [98] presented some complexity when considering birth weight. Including both typical and atypical antipsychotic medications in this analysis led to a slight reduction in the birth weight of babies born to treated mothers, but the mean difference was small: 57.9 g. This analysis showed a relationship between antipsychotic exposure of all kinds and small-for-gestational-age infants, but not for large-for-gestational-age infants, again not separating the effects of typical and atypical agents. This analysis noted that heterogeneity between studies existed in relation to reporting of smoking status, obesity, alcohol use, illicit drug use, socioeconomic status, confounding by indication or concomitant medication use, all of which are known to affect all parameters studied. Virtually none of the studies reported doses, which could also affect the risk to the exposed foetus. Interestingly, these authors took issue with the "typical/atypical" division commonly used in analysing antipsychotic medications, noting that both groups include a diversity of medications which can have different risks associated with their use. These authors advocated drug-specific data reporting, to help clarify the true risk presented by each medication.

The study by Bellet et al. [73] found a significant increase in the rate of preterm birth (16.4%, OR 2.57, CI 1.06–6.27) in babies exposed to aripiprazole. There was also a significantly increased rate of foetal growth retardation in the exposed group (OR 2.97, CI 1.23–7.16). There was a slightly reduced mean weight in exposed neonates compared with their peers (3268 g compared with 3339 g).

7.11.9 Studies Comparing First (Typical)- and Second-Generation (Atypical) Antipsychotics and the Risk of Prematurity

Petersen et al. [36] found that babies of women taking typical antipsychotics in pregnancy appeared at higher risk of prematurity or low birth weight (11.8%) than those taking atypical antipsychotics in pregnancy (8.4%) and much higher risk than those never exposed to antipsychotic medication (3.9%). Habermann et al. [21] found those exposed to first-generation antipsychotics had higher rates of premature birth (15.7%) than either women taking second-generation antipsychotics (9.2%) or those unexposed to any antipsychotic in pregnancy (8.7%) and that this difference was statistically significant (OR 1.96 first-generation antipsychotic vs. unexposed cohort, 95% CI 1.29–2.98), also citing similar results in Lin et al. [37]. One confounding variable raised by Habermann's group was the very high rate of concurrent antidepressant use in the cohort treated with first-generation antipsychotics, which could also have an effect on preterm birth.

The 2015 meta-analysis by Coughlin et al. [98] showed a statistically significant increase in rates of preterm birth of babies exposed to both typical and atypical antipsychotics in utero, but these studies were heterogeneous. It seemed that the impact of antipsychotic exposure in pregnancy on gestational age at delivery was present, but small, leading to babies born a mean of 0.21 weeks earlier.

In passing (as their focus was on weight at term birth) Newham et al. [25] excluded from their sample 16% of infants exposed to typical antipsychotics and 17% exposed to atypical antipsychotics, who were delivered prematurely. They compared this group with a reference group of unexposed infants, of whom 2% were premature and 5% were postdates. This result contrasts with the study by Brunner et al. [85] using the Eli Lilly reporting database on olanzapine, which found rates of premature birth of 9.8% in these babies compared with a population rate of 12.8%.

Kulkarni et al. [4] did not stratify their results according to antipsychotic class, noting that a large majority of their cohort took atypical antipsychotics. Interestingly, these authors stratified by dose and found that dose of antipsychotic (measured in risperidone equivalents) correlated inversely with prematurity. Babies born at term were exposed in the first trimester to an average of 2.6 mg risperidone equivalent dose, whereas babies born prematurely were exposed to an average of 5.0 mg, $p = 0.02$.

7.12 Second-Generation Antipsychotics and High-Birth-Weight Infants

7.12.1 The Influence of a Diagnosis of Mental Illness: Schizophrenia

Vigod et al. [72] did not subcategorise women's treatment medication but considered all women with a diagnosis of schizophrenia together. In this cohort they found

that 4.5% of babies born to women with schizophrenia were born at larger than the 97th centile, compared with 2.7% in the referent group. This comparison was adjusted for maternal age, parity, income, community size, pre-existing diabetes, hypertension, thromboembolic disease and infant gender. The adjusted odds ratio for this was 1.53 (1.17–1.99).

7.12.2 Second-Generation Antipsychotics and High-Birth-Weight Infants

The same group subsequently more closely examined the nexus between treatment of mental illness in pregnancy and large-for-gestational-age babies [39]. Focusing on atypical antipsychotic use, this study showed an increase in high-birth-weight (>97th centile) babies born to the cohort treated with atypical antipsychotics compared with the unmatched general population. However, when matched for health service usage and demographics, this outcome was no longer significantly different in the treatment group, suggesting that lifestyle risks associated with a diagnosis of mental illness could also be responsible for the discrepancy.

Habermann et al. [21] did not find a significant increase in birth weight of babies exposed to second-generation antipsychotics in utero in comparison with controls. Similarly, Reis and Kallen [20], observing a cohort of women taking both first- and second-generation antipsychotics for their mental health, did not find a significant increase in rates of high birth weight.

Boden et al. [1, 2] did not separately examine the effect of antipsychotics on birth weight. However, treatment of women with bipolar disorder with mood stabilisers including antipsychotics resulted in a non-statistically significant increase in the risk of large-for-gestational-age infants. The authors' hypothesis, that macrocephaly might relate to specific medications (olanzapine and clozapine) seemed to be borne out in the results of the second study undertaken by this group, in women taking antipsychotic medication. The most striking finding was that this group of infants had an adjusted OR of 3.02 (1.60–5.71) for head circumference of more than two standard deviations from the average. This was such an unusual finding that the authors assessed for the possibility that hydrocephalus might account for the difference, which it did not.

Sadowski et al. [26] found that babies born to women taking second-generation antipsychotics in pregnancy were more likely to be large-for-gestational-age (>90th centile), at $p < 0.05$. However, after analysing for treatment effect, this group felt that the major predictor of large-for-gestational-age babies was pre-pregnancy weight of the mother. Notably, this does not discount the effect of second-generation antipsychotics on this outcome but suggests that the impact may occur prior to conception.

The blockbuster study in this area is Newham et al. [25] with results that, if replicated, have significant implications for medication choices in treating women with multiple risks for obesity in pregnancy. Newham et al. [25] note

that, aside from the putative effect of atypical antipsychotic medication, risk factors for macrosomia at delivery are maternal obesity, type I diabetes, gestational diabetes and excess pregnancy weight gain. This group focused on gestational weight at term delivery, excluding all women with a diagnosis of diabetes, those whose babies had congenital malformations or who were taking both a typical and atypical antipsychotic medication. Large and small for gestational age were defined as below the 10th or above the 90th centile. Newham et al. [25] found a highly significant increased rate of large-for-gestational-age infants in the group exposed to atypical antipsychotics (20%) than in both the typical antipsychotics (2%) or the reference unexposed group (3%), $p < 0.05$. This difference was even more marked when the babies exposed to olanzapine and clozapine were compared with the reference group. Of these babies, 31% were large for gestational age. Notably, this study did not record maternal smoking or alcohol use, which they considered a limitation. These authors also considered a cohort effect on infant size over time, as rates of obesity in women have increased over that time period.

They further note that large-for-gestational-age infants can cause their own complications at delivery for the mother including vaginal lacerations, postpartum haemorrhage and increased risk of emergency caesarean section. Risks for the baby cited by Newham et al. [25] include birth trauma, shoulder dystocia and foetal hypoxia, as well as risks for higher BMI and greater incidence of diabetes in later life.

7.13 Neonatal Distress and Adverse Neonatal Events

7.13.1 Definitions

There is a plurality of names for the cluster of signs and symptoms that may manifest when placental transfer of a substance and its metabolites comes to an abrupt end at delivery. Habermann et al. [21] note the difficulty in comparing rates of neonatal distress due to the absence of an internationally agreed measure or scale for these events.

Convertino et al. [113] hypothesise that this cluster may represent either the residual toxic effects of a substance which is no longer efficiently metabolised by infant kidneys and liver or alternatively a withdrawal from a high blood level of a substance which is no longer available. These authors suggest that in the case of antipsychotics, some symptoms occur as a consequence of cholinergic rebound, and others relate to dopamine blockade. The multiple names for this syndrome include “neonatal abstinence syndrome”, “neonatal withdrawal syndrome”, “neonatal adaptation syndrome” or “neonatal behavioural syndrome” and in the case of antipsychotics, encompass a range of symptoms and signs including agitation, feeding disorders, abnormalities of tone, respiratory distress, somnolence and tremors [39]. They can appear within hours after delivery, and some reports suggest that they can remain up to a month afterwards [39].

7.13.2 The Influence of Diagnosis of Mental Illness on Adverse Events at Delivery

Reis and Kallen [20] found increased rates of low APGAR scores, respiratory diagnoses and hypoglycaemia in the babies of women treated with antipsychotics for mental illness, but none of these differences reached significance. These scores were adjusted for maternal age, parity, smoking and history of prior miscarriage.

Babies whose mothers had either treated or untreated bipolar diagnoses [1, 2] had a diverse APGAR range, which was difficult to interpret. Babies whose mothers were not treated seemed more at risk of low APGAR though this difference did not reach significance; babies whose mothers were treated with medication did not seem to be as much at risk of low APGAR as the general population. Boden et al. [1, 2] also examined the risk of neonatal hypoglycaemia; both treated and untreated populations were more highly at risk for this outcome, though this risk only reached significance in the untreated cohort.

Jablensky et al. [15], focusing on risks relating to underlying maternal diagnoses of psychiatric illness, noted that there was a trend towards lower APGAR score at 5 min, respiratory depression and intubation in babies of women with schizophrenia. Matevosyan [24] echoed this outcome, finding a statistical increase in rates of low APGAR scores at 5 min for babies of mothers with schizophrenia.

Vigod et al. [72] found a highly elevated risk of neonatal abstinence syndrome for babies of mothers with schizophrenia (aOR = 53.7, 95% CI = 36.8–78.4). In this research, neonatal abstinence syndrome is classified separately from respiratory distress syndrome, which these authors also found more commonly in babies of mothers with schizophrenia (aOR = 1.86, 95% CI = 1.23–2.81), as were seizures (aOR = 4.21, 95% CI = 2.31–7.65), intraventricular haemorrhage (aOR = 2.43, 95% CI = 1.34–4.41) and persistent foetal circulation (aOR = 3.19, 95% CI = 1.43–7.14).

The fascinating coda to this alarming warning was that, on re-examining the data and matching with controls with similar patterns of healthcare utilisation [39], these differences became less marked. When these data were also controlled for the use of psychotropics other than antipsychotic medications, in particular antidepressants, mood stabilisers and benzodiazepines, these outcomes lost significance. Regardless, the authors argue that these women and their babies are still at much higher risk of adverse outcomes than the general population and hence should be observed and supported much more closely. It seems, however, on the basis of this analysis, that it is not necessary to avoid the use of antipsychotics for these women, which should help maintain mental stability throughout pregnancy and beyond.

7.13.3 First-Generation Antipsychotics and Adverse Neonatal Events

There has been awareness of the possibility of withdrawal syndromes and extrapyramidal side effects from antipsychotic use in pregnancy for many years ([114], via [36]). More recently, both the US Food and Drug Administration and the UK

Medicines and Healthcare Products Regulatory Agency updated their advice on risks of extrapyramidal effects and withdrawal syndromes in 2011 in regard to typical antipsychotic medication use in pregnancy. Advice from the US FDA was based on 69 cases reported between 2008 and 2011. Symptoms included agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder.

Einarsson and Boskovic [92], completing an exhaustive review of all known studies relating to antipsychotics in pregnancy, found a paper from 1971 which described neonatal withdrawal and extrapyramidal symptoms in babies exposed to higher doses of chlorpromazine, up to several weeks after birth [115]. These authors note other reports of extrapyramidal side effects after exposure to typical antipsychotics which persisted up to months after delivery [116] and two reports of paralytic ileus in neonates after exposure to typical antipsychotics [114].

7.13.4 Adverse Events Associated with First- and Second-Generation Antipsychotics: Is This a Useful Distinction in Assessing Risk for Neonates?

Convertino et al. [113] notes that both first-generation and second-generation antipsychotic use in later pregnancy have been associated with increased rates of abnormal neuromotor performance, hypertonicity and tremors. These authors mention in this context the 2011 USFDA warning, mentioned above. Convertino et al. [113] also mentioned results from Kulkarni et al. [4] in the Australian National Register of Antipsychotic Medications in Pregnancy (NRAMP) of rates of medical withdrawal symptoms in 15% of babies, which appeared to be dose-related and which took up to 6–8 weeks to subside. Kulkarni et al. [4] noted that there was a trend towards exposure to higher doses of medication at 12 weeks' gestation in babies who experienced withdrawal symptoms ($p = 0.162$).

Interestingly, Convertino et al. [113] also drew some distinctions between reported symptom profiles after withdrawal from specific medications: seizures in one case of a baby exposed to risperidone and heat regulation, hyperbilirubinaemia and feeding difficulties in another. These authors note case reports of thermoregulation difficulties, tremor, vomiting, poor feeding and decreased muscle tone in haloperidol; respiratory distress, hypotonia and poor feeding in olanzapine; and retinopathy and transient neonatal hypoxaemic encephalopathy in clozapine. They also note a report of delayed neurological and extrapyramidal symptoms in fluphenazine, presenting a month after delivery. Worsley et al. [117] commented on outcomes for 114 babies in the NRAMP database referred to above. In this analysis, babies who were exclusively breastfed from delivery (12.2%) were less likely to have withdrawal symptoms than babies who were exclusively bottle-fed (27.5%), with OR 2.74, CI 1.02–7.32 and $p = 0.04$. A full discussion of this issue is beyond the scope of this chapter; however, it remains an interesting outcome when considering ways to reduce the impact of adverse events on neonates.

Sadowski et al. [26] found higher rates of foetal distress at delivery amongst women exposed to second-generation antipsychotics than in those unexposed

(though this did not reach statistical significance). This group also had much higher rates of Neonatal Intensive Care Unit (NICU) admission, at 25.3% vs. 9.5%, and much greater rates of signs of neonatal abstinence syndrome (which they labelled "PNA") (16.5% vs. 5.2%). These researchers considered PNA to include central nervous system, respiratory and gastrointestinal problems.

The 2007 study by Newport et al. [35] demonstrated APGAR at 5 min to be broadly similar across all treatment groups, with a mean between 8 and 9. Olanzapine and quetiapine were associated with higher rates of NICU admissions (30.8% and 9.5%, respectively), both of which are higher rates than those observed in the general population. Notably, again, olanzapine seemed to be associated with a higher rate of cardiovascular and respiratory complications, with 23.1% and 30.8% of babies experiencing these adverse outcomes at delivery.

Gentile's 2010 [16] review found high rates of neonatal adverse events in babies of mothers taking clozapine in pregnancy, including transient floppy infant syndrome, noting that most of these women were also taking other medications. He found 63 of 419 babies exposed to olanzapine who experienced "perinatal complications", not further specified. He found neonatal complications in babies exposed to risperidone, including withdrawals and seizures, but did not further characterise these. He also found reports of neonatal adverse events relating to late-pregnancy use of chlorpromazine including extrapyramidal signs, respiratory distress, seizures and transient neurodevelopmental delay.

7.13.5 Aripiprazole and Adverse Neonatal Events

Bellet et al. [73] found two babies who experienced neonatal adverse events associated with aripiprazole exposure. The first had a withdrawal syndrome with pulmonary hypertension and respiratory distress. The second had an aspiration pneumonia in the context of premature rupture of membranes. More generally, APGAR scores were lower at both 1 and 5 min in babies exposed to aripiprazole.

7.13.6 Clozapine and Adverse Neonatal Events

Isolated case reports of reduced heart rate variability have been noted in foetuses of women taking clozapine in pregnancy [118, 119]. There have been several case reports of floppy infant syndrome in babies exposed to clozapine in utero [120, 121]. The longer-term sequelae of this syndrome can include motor delay and other developmental difficulties [122]. Seizures have been reported in clozapine-exposed babies [121, 123]. The authors speculated that these could result from immature infant hepatic metabolism, or alternatively from withdrawals from the medication, given that some seizures have occurred several days after delivery. There have been several reports of shoulder dystocia, suggesting possible macrosomia at delivery [124, 125].

Reports of agranulocytosis of babies breastfed by mothers taking clozapine [105] suggest that this effect could also occur as a consequence of treatment in utero. On

this basis, Kulkarni et al. [27] have suggested that weekly white cell monitoring should occur up to 6 months after delivery for babies exposed to clozapine in utero.

7.13.7 Lifestyle Factors Elevating Risk of Adverse Neonatal Events

Whereas the absolute rates of adverse neonatal events were higher in babies of women taking antipsychotics throughout pregnancy at 6% in the 2016 study by Petersen et al. [36], it is notable that 4.7% of babies of women not taking antipsychotics in pregnancy, but who had previously been prescribed these, also experienced these outcomes. Rates of adverse neonatal events for babies of women never exposed to antipsychotics were much lower, at 2.5%. After adjustment for age, obesity, alcohol problems, smoking, illicit drug use and antidepressant and anticonvulsant prescribing, the differences between these groups were not significant. These results raise the issue, also raised elsewhere, of the contribution of underlying illness or clustering lifestyle factors to adverse outcomes, rather than solely relating to the administration of medication itself.

7.13.8 Polypharmacy Escalates Risk of Adverse Neonatal Events

Coppola et al. [100], considering only risperidone, noted 1 of 68 pregnancies in which the baby experienced a possible withdrawal syndrome. The mother of this child was also taking imipramine, clonazepam and alcohol through pregnancy. The baby experienced sleepiness, jitteriness and slow sucking but did not require transfer to a NICU or special care nursery. These authors also found 21 of 197 retrospectively reported pregnancies exposed to risperidone which reported adverse neonatal events. These included drug withdrawal in 13 (in five of which drug withdrawal was attributed to other drugs taken by the woman in pregnancy), movement disorder or tremor in nine, jitteriness or irritability in eight, feeding problems in eight, somnolence and lethargy in three and seizures in three. Eighteen of the 21 were complicated by concomitant use of other drugs, illicit or prescribed, known to be associated with withdrawal syndromes. Three of these babies were transferred to NICU for further care; three required oxygen, tube feeding or treatment with anticonvulsants; and 15 did not require any specific treatment.

Consistent with these findings, Sadowski et al. [26] found that adverse neonatal events were much more common in those exposed to polypharmacy, with signs at 21.2% vs. 4% of monotherapy babies and NICU admission at rates of 28.8% vs. 16%. When those exposed to polypharmacy were excluded, babies exposed to second-generation antipsychotics had similar rates of abstinence symptoms to those in the unexposed group. Similarly, Diav-Citrin et al. [84] found that the rate of neonatal adverse outcomes was 5% in a cohort treated with haloperidol. Most of these babies were born to women treated with multiple psychotropic medications. The cohort examined by Kulkarni et al. [4] also

demonstrated high rates of polypharmacy, with 11% of women taking an additional antipsychotic medication and 43% of women prescribed with antipsychotics also taking an antidepressant. This study found a strikingly high rate of neonatal respiratory distress in babies exposed to these multiple medications, at 37%. The authors noted that babies also exposed to mood stabilisers were over six times more likely to experience respiratory distress. Overall, these babies were also sicker than most other cohorts examined; over 40% required transfer to a neonatal ICU or special care nursery (SCN), compared with expected community rates of 14.2%. The authors noted that higher doses of antipsychotics in pregnancy increased the risk of admission to NICU or SCN.

The 2013 study by Habermann et al. [21] adjusted for alcohol consumption, smoking and gestational age at birth, all of which were shown to have a significant effect on neonatal adverse events. After adjustment, exposure to second-generation antipsychotics was also significant in this regard (OR = 6.24, 95% CI = 3.51–11.10) as was exposure to first-generation antipsychotics (OR = 5.03, 95% CI = 2.21–11.44). The outcomes measured for newborns included jitteriness, somnolence and seizures. The authors noted that co-medication with additional psychoactive medications greatly added to the risk of postnatal disorders for all babies exposed to antipsychotics in utero, raising rates from 10.8% and 10.3%, respectively, to 29.5% and 36.4%. Hence polypharmacy appears to dramatically escalate the risk of neonatal morbidity in these vulnerable babies. The medications most associated with neonatal symptoms included quetiapine at 25.8% and aripiprazole at 23.5%, followed by olanzapine at 15.1%. As a consequence of these very marked results, Habermann et al. [21] recommend that babies born to women taking any antipsychotic medication in the final week of pregnancy should have their delivery planned with access to a neonatal intensive care unit.

7.14 Neurocognitive Development of the Infant

7.14.1 Risk of Developmental Delay and Autism Spectrum Disorders in Babies Exposed to Antipsychotics In Utero: What Is the Contribution of Underlying Mental Illness in Parents?

Amongst concerns about toxicity exposure and risks in pregnancy are the concerns about increased risk for autism spectrum disorders in the offspring of women exposed to these agents. Scandinavian research indicates that mental illness itself confers an increased risk of autism spectrum disorders in the children of those with schizophrenia, affective disorders and substance abuse disorders ([126], via [127]). Other studies found similarly that maternal and paternal schizophrenia spectrum diagnoses, maternal depression and personality disorder diagnoses were all associated with autism spectrum disorder in children [128].

Jokiranta et al. [127] examined all live births in Finland over 18 years. They considered confounders including parental age, smoking in pregnancy and

small-for-gestational-age births, finding autism spectrum disorder was associated with maternal schizophrenia, mood, anxiety, personality, substance use and childhood disorder diagnoses (i.e. all diagnostic categories). A child was at significantly greater risk of autism spectrum disorder if both parents had a mental health diagnosis (with over threefold increase in risk). The strongest association was found between schizophrenia spectrum disorders and pervasive developmental disorder not otherwise specified. Mood disorders were the only categories of psychiatric illness found to be associated with every subcategory of autism spectrum disorder.

7.14.2 Is There a Differential Effect of Antipsychotics In Utero on Neurocognitive Outcomes of Exposed Babies of Mothers with Mental Illness?

Morgan et al. [129], examining a Western Australian data set, found similarly that pervasive cognitive deficits appear to cluster with schizophrenia and also found that timing of onset of illness (prior to or after the birth of offspring) did not impact outcomes, suggesting that maternal medication use in pregnancy was not a factor in later development of pervasive developmental difficulties in exposed babies. This study found that children of women with schizophrenia, bipolar disorder and major depressive disorder were up to three times more likely to have a diagnosis of intellectual disability compared with their peers. Severity of maternal illness and paternal history of psychiatric illness were found to be independent risk factors in this relationship, suggesting a genetic influence. In support of this theory, authors cited deletions in common at 15q13.3 in people with schizophrenia, autism and epilepsy.

7.14.3 What Is the Effect of Antipsychotic Exposure In Utero on Neurocognitive Outcomes?

In a recent systematic review, Gentile and Fusco [130] evaluated the current literature on neurodevelopmental risks of antipsychotic medication in pregnancy and found it lacking. These authors found only 29 articles providing original data: 18 case reports, seven case series, two case control studies, one prospective and one retrospective study. At that point, amisulpride, aripiprazole, risperidone (including long-acting injection), paliperidone, ziprasidone, haloperidol and zuclopenthixol were only evaluated through case report data. Of these, many women described in case reports were also taking other psychotropics of the same and different classes and had diverse underlying illnesses, including pseudotumour cerebri. Olanzapine and quetiapine were more extensively studied. Coppola et al. [100], commenting specifically on risperidone, cited four retrospective case reports of developmental difficulties in the first year of life, which could not be further explored: one case of "developmental delay", "neurodevelopmental problems", "motor problems at 8 months of age" and "muscle problems at 6 months of age". There is a paucity of

data on this issue. Karakula's 2004 [121] case vignette reported developmental delay at 7 months in a baby exposed to clozapine in utero who experienced seizures and encephalopathy at birth. Mendhekar [131] reported on isolated speech delay in a child exposed to clozapine in utero and through breastfeeding apparently otherwise developing normally.

There remain several well-conducted studies worth highlighting in this discussion, however. Shao et al. [132] followed a cohort of women taking second-generation antipsychotics in pregnancy who, unusually, did not take other psychotropics. These authors excluded babies with congenital malformations or birth complications and followed the remaining 58 babies to 12 months of age. No woman breastfed for more than a month. Notably, the babies born to mothers taking clozapine performed more poorly on the Bayley Infant Neurodevelopment Scale than their peers taking olanzapine, risperidone or quetiapine at 2 and 6 months, but these differences evaporated at 12 months. Additionally, it was noted that the women taking clozapine had significantly longer premorbid periods of illness than other mothers taking part in the study.

Peng et al. [5] compared a cohort of 76 babies whose mothers had taken an atypical antipsychotic medication throughout pregnancy, with a cohort of matched infants without uterine exposure. These babies were also assessed using the Bayley III at 2, 6 and 12 months. These showed similar results to Shao et al. [132]; whereas there were scores indicating delay in cognitive, motor, socioemotional domains and adaptive behaviour in babies exposed to atypical antipsychotics in utero when compared with their unexposed peers, these differences had disappeared at 12 months. There were no significant differences at any time point in language, body weight or height between exposed babies and their peers. Notably, these babies were matched with babies of mothers with no mental illness, of similar age and education level. Mothers with a diagnosis of schizophrenia were more likely to have had an unplanned pregnancy, less likely to take folate or vitamins and less likely to work in pregnancy, consistent with other research. These women were also more likely to have a BMI >23.9 (the marker for overweight used in China). These babies were less likely to be breastfed, which along with the use of antipsychotics in pregnancy appeared to have a significant effect on cognitive and other domain performance at 2 and 6 months. These authors were surprised by the lack of adverse findings in this group, given the multiple other confounding variables which could have led to a poorer outcome for babies of women taking antipsychotics in pregnancy. They suggested the possibility of a neuroprotective effect of antipsychotics on babies' development in pregnancy, citing animal studies by Park et al. [133] and Gassó et al. [134].

Kulkarni et al. [4] followed 100 infants of mothers taking antipsychotics and other psychotropics in pregnancy. These women were assessed for mental health in pregnancy and postpartum using the Positive and Negative Syndrome Scale (PANSS) for psychotic symptoms and the Edinburgh Postnatal Depression Scale (EPDS) for depressive and anxiety symptoms. Medication doses in pregnancy were measured in risperidone equivalents. Notably, 39% of women tested had scores at or above 10 on the EPDS at 6 weeks postpartum, suggesting the presence of depressive or anxiety symptoms which could in turn impact on infant performance and

development. At 1 year postpartum, most mothers studied were well and caring for their babies, though few had returned to paid work. Of the 100 babies studied, 96 were progressing well, whilst four were undergoing assessment or treatment.

Johnson et al. [135] examined infants of mothers taking antipsychotics and antidepressants in pregnancy, in comparison with an unexposed cohort. Parents were also administered the Beck Depression Inventory and the Structured Clinical Interview for DSM IV-TR to ascertain parental psychiatric diagnoses. Babies aged between 4 and 6 months performed a neuromotor and habituation task. Babies of mothers who took antipsychotics in pregnancy performed more poorly on this task. The implications of this isolated result for overall performance in cognitive, interpersonal, emotional and motor domains are unclear. It would be interesting to see whether this poor performance was sustained at 12 months or if the difference became attenuated, consistent with Shao et al. [132] and Peng et al. [5].

7.15 Conclusion

A woman with a diagnosis of major mental illness facing pregnancy also faces a host of related challenges which includes the direct effect of her illness on her mental and physical health and that of her baby and also the social and economic disadvantage that this illness confers.

There is a broad consensus on important contributing factors to adverse outcomes for women in this population: poorer general health in women suffering major mental illness including high rates of obesity and diabetes and increased rates of smoking, alcohol and illicit drug use. For pregnant women in particular, factors contributing to adverse outcomes include reduced attendance at antenatal appointments; reduced use of prenatal vitamins, folate and thyroid hormone; increased rates of unplanned and unwanted pregnancy; limited social support; and increased rates of domestic abuse, poverty and disadvantage.

The study of the impact of antipsychotic medications in pregnancy is complicated by the imperative for many women to remain well in pregnancy and the postpartum. Multiple potential error sources in data derived from these women include confounding by indication; such confounders already identified include severity of illness, socioeconomic, historical or lifestyle factors and detection bias.

What is striking about recent research is that more sophisticated methods of analysis suggest that problems relating to the experience of disadvantage for women with a major mental illness may actually form a significant aspect of the negative outcomes measured for these women [39]. There are two further conclusions that can be drawn from this: firstly, that harms previously attributed either to the illness itself or to antipsychotic medication treatment may actually relate to socioeconomic factors.

Secondly, if a more holistic approach to support of these women in pregnancy included efforts to avert homelessness, identify and protect against physical abuse, support the use of prenatal vitamins and reduce incidence of smoking, alcohol and drug use, a large proportion of the harms to the foetus and baby could be minimised.

Hence care in pregnancy for women with a major mental illness needs to encompass far more than just careful prescribing of appropriate medications; this is only the first step in averting harm. As psychiatrists, we must advocate for the best practice in using evidence-based prescribing as part of an overall care package which incorporates these other elements as well.

Emerging evidence does suggest that iatrogenic harms can accrue to the mother and her baby from psychotropic medication treatment. In the case of antipsychotic medication, the harms seem to be becoming more clearly defined. In the first instance, the risk of harms to women appears to be shifting slightly over time. Whereas the risk of reduced fertility from hyperprolactinaemia was previously highly prevalent and associated with first-generation antipsychotic medication [50], reproductive risks in the era of widespread use of second-generation antipsychotic medication relate more to the risks associated with obesity and diabetes in pregnancy [25].

A common thread in several recent research papers is the risk of pre-pregnancy weight gain for subsequent development of gestational diabetes. This suggests that this risk should be considered for every woman with reproductive potential suffering a major mental illness from the age of 15–50. This is especially important given the increased rates of unplanned pregnancy in this group. The cascading risks relating to obesity and gestational diabetes for both mother and baby in pregnancy include increased rates of congenital malformations and macrosomia, increased rates of instrumental delivery and emergency caesarean section and increased rates of transfer to neonatal intensive care.

Despite these associated risks, the risk and rate of major congenital abnormalities relating directly to exposure to antipsychotic medications in pregnancy do not seem to be significantly elevated [34]. However, rates of neonatal distress and withdrawal symptoms are high in these babies and seem to be higher for some antipsychotic medications than others. There is some very limited research to suggest that there is also a dose-related increase in these symptoms.

Notably, in addition to all the socioeconomic harms previously mentioned, these babies are very rarely exposed to just one medication or just one class of medications. The dramatically elevated risk of neonatal adverse events is severe enough to prompt transfer to a NICU occurs in the context of polypharmacy [26]. This is a harm that can be greatly curtailed by sensible, sparing prescribing of only those medications (such as antipsychotics) which are required to maintain a stable mental state. The high rates of transient adverse outcomes at delivery for these babies also suggest that babies of women prescribed with psychotropics in pregnancy should be delivered in a centre with access to neonatal resuscitation and intensive care support [21].

There is a positive note in this discussion that neurodevelopmental studies, limited though they are, suggest that developmental delay noted in babies exposed to antipsychotics in pregnancy is unlikely to persist to 1 year postpartum, despite high rates of psychiatric symptoms in women in the first year after delivery [4]. What is lacking is further longitudinal follow-up of this cohort which might provide more meaningful results relating to cognitive, emotional and behavioural performance at school entry or beyond.

In concert with a more sophisticated approach to modelling and analysis, borrowing approaches from other research fields such as health economics (high-dimensional propensity scoring, for example, or machine learning techniques), several authors have called for a more sophisticated approach to research in psychotropics [16, 21, 113]. It is probably not good enough to lump antipsychotic medication into two baskets and analyse harms associated with each; individual drugs within both novel and older antipsychotic groups have specific modes of action and associated risks which may be distinct and whose specific harms may be masked by considering them all together.

The future of best practice care for women with a major mental illness in pregnancy and the postpartum incorporates careful analysis of both large population-based data sets and granular review of symptoms and side effects in long-term follow-up studies of mother and baby pairs to inform prescribing practice. Consideration of a woman's reproductive health should be integrated into her care throughout her life, and the care of mothers and babies in the context of maternal mental illness should be a trigger to provide enhanced social, emotional, economic and psychiatric support to avert harm and improve outcomes.

Expert recommendations based on scientific evidence and clinical experience
• Preconception planning for women with major mental illness includes contraception and fertility advice and management in addition to medication safety advice in pregnancy • Women with major mental illness require both physical and mental health monitoring throughout pregnancy • Physical health issues to address with women presenting with major mental illness in pregnancy include – Support around smoking, drug and alcohol use cessation – Prenatal vitamin supplementation – Evidence-based advice around medication safety Avoid or minimise polypharmacy and switching medications
• Mental health monitoring and support include additional support for social safety, including detecting and addressing issues of homelessness, domestic abuse and social disadvantage or poverty • Assess for and address obesity in all women of childbearing age who present with a major mental illness • Monitor and manage obesity in pregnancy for women taking antipsychotic medications • Assess for and manage diabetes in pregnancy for women taking antipsychotic medications, including liaison with expert medical teams • Antipsychotic medication and congenital abnormalities – Whereas the data does not at this stage suggest significantly increased risk of structural abnormalities for babies exposed to antipsychotic medications in utero, the evidence base is small
• Antipsychotic medication can increase the risk for premature birth, low-birth-weight or small-for-gestational-age infants or high-birth-weight infants. • Consider intrauterine ultrasound for structural and growth abnormalities in all babies exposed to antipsychotic medication in utero. In particular, consider high resolution ultrasound for cardiac defects at 20 weeks and at 36 weeks • A baby exposed to antipsychotic medications in utero is at increased risk of neonatal withdrawal symptoms and distress; ensure that tertiary neonatal support is available at delivery • There is at present no strong evidence supporting developmental delay or disadvantage for babies exposed to antipsychotic medication in utero

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Antipsychotics and Lactation

8

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8.1 Introduction

The Centers for Disease Control and Prevention estimates that 79% of women in the United States attempt breastfeeding in the postpartum period [1]. While the American Academy of Pediatrics recommends exclusive breastfeeding for about 6 months, followed by continuation of breastfeeding along with complementary foods for 1 year or longer, data suggest that only 49% of infants are breastfed until 6 months of age [1, 2]. For women with psychiatric disorders, only half of women—regardless of psychotropic medication used during pregnancy—attempt to breastfeed [3]. Other studies have reported the rate of breastfeeding among mothers with mood disorders such as bipolar disorder to be significantly lower at 15% [4]. There are a variety of potential factors contributing to breastfeeding trends, including maternal intent to breastfeed prior to delivery, a sense of self-efficacy regarding breastfeeding, perceptions of sufficient milk supply (that may or may not correlate with physiologic sufficiency), hospital support for infant rooming, and safety concerns regarding exposures to psychiatric medications [5]. Additionally, mothers may not be encouraged—or perhaps even discouraged—to breastfeed while on psychotropic medications by medical staff for a variety of reasons including lack of data, safety concerns for the infant, and/or negative attitudes and bias toward mental health and psychotropic medications in general [6]. Regardless, rapid resumption or continuation of psychotropic treatment in the postpartum period is essential to mitigate risk of symptomatic relapse of the mother's mental illness [7].

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The relationship between untreated maternal mental illness, specifically psychosis and bipolar disorder, and later childhood outcomes is difficult to assess due to methodological constraints and sample sizes too small to significantly power a study. A few studies, primarily focusing on maternal depression, have tried to overcome these limitations [8]. In a recent comparison of infant outcomes between pharmacologically treated and untreated mothers with bipolar disorder, there was no consistent relationship between maternal mental illness and delay in the child's development [3]. However, other studies have shown an increased risk of microcephaly and intellectual disability in children born to women with bipolar disorder [9, 10]. Moreover, severity of parental mental illness at the time of the pediatric evaluation has been shown to be more predictive of children's behavioral profile than mental illness severity at the time of pregnancy and birth [11, 12]. Given these studies' discordant results, it is challenging to ascertain a child's true risk of significant neurodevelopmental impairment following prenatal atypical antipsychotic exposure relative to exposure effects of parental mental illness at various points in development.

Despite these aforementioned discordant results, untreated maternal mental illness can have a profound effect on maternal and neonatal morbidity and mortality, with estimates of infanticide around 5% and maternal suicide around 4% [13]. As women with mental illness are at greatest risk for depression and psychosis during the postpartum period [7], standard-of-care pharmacologic treatment of psychiatric illness is most assuredly indicated. Unfortunately, there is a lack of prospective observational data assessing risks to the neonate exposed to antipsychotics through breastfeeding. Furthermore, most studies of medications and lactation are not sufficiently powered enough to draw statistically meaningful conclusions [14]. Nevertheless, lactating mothers require appropriate psychiatric care during the postpartum period. With respect to nursing while on antipsychotics, thoughtful risk/benefit assessment is recommended, evaluating such factors as maternal preferences, infant and maternal benefits of breastfeeding, and the known and unknown risks of medication exposure for the baby via breast milk, maternal illness history and stability on and off psychotropics, the infant's health status, and the potential negative consequences of breastfeeding on maternal sleep deprivation/disruption. Ideally, such a discussion should occur in advance of delivery with the patient, her psychiatrist, and pediatrician. In this chapter, a brief overview of general pharmacological and clinical considerations, regarding the use of antipsychotics during breastfeeding, will be presented. Commonly used first- and second-generation antipsychotics (FGAs and SGAs) will be critically evaluated to determine whether neonatal exposure through breast milk poses a significant risk in terms of adverse effects.

8.2 Pharmacological Considerations

Efforts have been made to quantify the amount of psychotropic medications and their metabolites in the breast milk of nursing mothers. In order to more accurately measure the infant's exposure to medication, serum drug levels in the infant have

also been assessed. From the available data, it appears that all medications, including antidepressants, antipsychotic agents, mood stabilizers, and benzodiazepines, are secreted into the breast milk. While concentrations of these medications in breast milk vary considerably, they are, generally, substantially less than in utero exposure [15]. The amount of medication to which an infant is exposed depends on several factors: factors pertaining to the specific medication, the maternal dosage of medication, the frequency of dosing and infant feedings, and the rate of maternal drug metabolism. Standard parameters such as relative infant dose, milk/plasma concentrations, and infant drug plasma levels have been used in some reports to estimate the risk of medication exposure to the neonate through breast milk [16, 17]. A relative infant dose of less than 10% is generally considered compatible with breastfeeding [18].

As antipsychotics are generally metabolized by the liver, information regarding the physiology of the neonate is important when understanding differences in the reported relative infant dose in case reports and series. Hepatic biotransformation of phase I and phase II reactions are around 30% at birth and 30% at age 3 months, respectively, of adult functionality [19]. By age 1, the infant liver functions similar to adults. Furthermore, premature infant hepatic and renal system mature more slowly than newborn infants [16]. This information may be useful as it can help dictate the frequency of feedings, volume of breast milk consumed by the neonate, and timing of maternal medication consumption and breastfeeding [16]. For example, if the mother consumes the medication immediately before breastfeeding, the infant is less likely to be exposed to peak concentration of the antipsychotic in breast milk.

8.3 First-Generation (Typical) Antipsychotics (FGAs)

While FGAs such as haloperidol have been used for many years in pregnancy, there is a surprising dearth of information pertaining to infant safety in the setting of FGA exposure through breast milk [20]. The majority of literature derives from case reports and observational studies published in the last decade of the twentieth century [16]. However, the accumulated evidence suggests that FGAs are compatible with breastfeeding with low levels found in breast milk excretion and rare adverse events [13, 21].

8.3.1 Haloperidol

Regarded as one of the safest antipsychotics to use during pregnancy [13, 22], use of haloperidol during breastfeeding and concomitant data regarding infant exposure are limited. Nevertheless, data from observational studies including several case reports and an older open-label prospective controlled observational study suggest no acute adverse effects [16, 23–25]. Others have also noted that only small amounts of haloperidol are excreted into breast milk [26]. In an open-label study [25], infant

serum levels (0.8–8.0 ng/mL) ranged widely, with three infants exposed to a combination of haloperidol and chlorpromazine. No immediate side effects were noted in this cohort. Additionally, there were no psychomotor differences between study groups at 1–4 months of age. Later follow-up revealed normal psychomotor development in all but two infants who were exposed to a combination of antipsychotics (haloperidol and chlorpromazine) and scored on the borderline for developmental delay at 12 and 18 months of age per the Bayley Scales of Infant Development psychomotor development scales. In the case report from Whalley et al. [24] of one mother-infant pair, the mother was on 10 mg/day of haloperidol while breastfeeding immediately after birth and discontinued therapy after 6 weeks. Subsequent infant development was noted to be normal.

8.3.2 Chlorpromazine and Other FGAs

The estimated relative infant dose for chlorpromazine ranges from 0.03% to 1.3%, which is well below the recommended 10% value considered compatible with breastfeeding [20, 27]. In one study, four mother-infant pairs were assessed for use of chlorpromazine while breastfeeding, and three of the pairs were exposed to concomitant haloperidol during the study [25]. Chlorpromazine dosage ranged from 50 to 600 mg/day with infant chlorpromazine serum concentration recorded as ranging from undetectable to 0.7 ng/mL. No acute negative side effects other than possible drowsiness were noted. In addition, no psychomotor differences were noted between groups at 1–4 months of age. However, developmental delays were noted in infants exposed to both chlorpromazine and haloperidol. Thus, while levels in breast milk and adverse effects of exposure to chlorpromazine are low, close supervision with attention to drowsiness and development in the infant is recommended.

Other FGAs, such as trifluoperazine, perphenazine, and flupentixol, may also be compatible with breastfeeding. Again, the data are limited and based on a few case reports and small observational studies but suggest low levels of medication found in the breast milk and no acute adverse events [20].

8.4 Second-Generation (Atypical) Antipsychotics (SGAs)

SGAs are increasingly preferred over FGAs as first-line treatment in numerous psychiatric illnesses given a decreased risk of extrapyramidal side effects and their prolactin-sparing properties compared to FGAs [28]. Numerous studies have assessed risk of congenital abnormalities of neonates exposed to SGAs in utero, with no increased risk above the general population's baseline risk for major malformations [29]. Despite this information on maternal use of SGAs during pregnancy, there is a surprising scarcity of robust information on maternal use of SGAs during breastfeeding and concomitant effects on the neonate.

8.4.1 Clozapine

Case reports suggest that clozapine tends to accumulate readily in breast milk in a dose-dependent manner [16, 30]. However, the relative infant dose for clozapine is a modest 1.4% of the weight-adjusted maternal dose [20]. Perhaps because of the well-known side effect profile of clozapine including hematologic toxicity and seizure, large cohort studies evaluating pertinent information regarding breastfeeding (i.e., ratio of maternal serum, breast milk, and infant serum) and neonatal side effects do not exist. In case reports, one infant exposed during *both* pregnancy and breastfeeding through 1 year of age had noticeable delay in speech acquisition though no other neurocognitive or motor deficits [31]. Another case study reported clozapine exposure via breast milk was associated with agranulocytosis and somnolence [32]. Due to the potential serious risk for agranulocytosis and seizure in the exposed infant, the American Academy of Pediatrics notes concerns regarding infant exposure to clozapine in breast milk [33], and its use should be avoided during lactation [22].

8.4.2 Olanzapine

Of the SGAs, olanzapine has been the most widely studied with respect to breastfeeding [17]. The bulk of the current evidence suggests that olanzapine is compatible with breastfeeding [16]. The reported relative infant dose of olanzapine ranges from 0.3% to 4% of the weight-adjusted maternal dose with no acute adverse events reported [16, 20, 34–39]. Case reports vary regarding detectability of olanzapine in infant's serum with most studies and reviews reporting undetectable levels [16, 20, 37, 40]. In one mother-infant pair with maternal dose of olanzapine of 15 mg/day, the infant's olanzapine levels were modestly detectable in the neonatal period but absent at 4 months of age likely secondary to the maturing neonatal liver and its ability to metabolize the drug [41]. Regardless, the infant developed normally. Manufacturer's registries, which are subject to selection bias, report approximately 15% of infants exposed via breast milk experienced complications, such as irritability, somnolence, insomnia, and tremor [35]. In the Yoshida et al. [25] cohort, however, there was no difference in adverse effects and developmental outcomes in breastfed olanzapine infants compared to control infants (mean olanzapine dose of 6.25 mg/day) at 1–2 years of ages.

8.4.3 Risperidone/Paliperidone

As with the other atypical antipsychotics, information on infant exposure to risperidone via breast milk is sparse and derives from case reports and case series. Risperidone was previously considered not compatible with nursing, though this recommendation was based solely on the absence of data in the published literature [42]. Currently, lactation data are available for risperidone and its active metabolite

and demonstrate no adverse effects [16, 43, 44]. The relative infant dose for risperidone ranges widely from 2.3% to 9.1% of the weight-adjusted maternal dose, and infant plasma levels of risperidone and its active metabolite are very low to undetectable [16, 20, 44]. Furthermore, case reports and case series reveal low milk/plasma ratios below 0.5 [44]. In mothers prescribed up to 6 mg/day, no adverse effects have been reported in infants [16, 42, 43]. Given the above information, risperidone appears to be compatible with the breastfeeding. No information exists regarding the safety of paliperidone per se. Safety information may be surmised given that paliperidone is the active metabolite (9-hydroxyrisperidone) of risperidone [44].

8.4.4 Quetiapine

Based on case reports and series, quetiapine demonstrates low excretion into breast milk and a lack of reported adverse effects in infants and is considered clinically to be compatible with breastfeeding [16]. At 400 mg/day, the reported relative infant dose ranges from 0.07% to 0.1% [20]. Case series report that quetiapine was not secreted into breast milk at all at maternal daily doses <75 mg, and for higher maternal doses, infant dose was calculated to be less than 0.01 mg/kg [11, 16, 45]. In the Misri et al. [46] series of case reports, two infants of six were found to have mild developmental delays at age 12 months, but the persistence of these findings into later childhood remains unknown.

8.4.5 Aripiprazole

Sparse information is available for the use of aripiprazole during breastfeeding. Aripiprazole is present in human breast milk with relatively low milk-to-plasma ratios with no acute adverse effects [47–50]. Some authors report that aripiprazole-induced infant somnolence is plausible [51, 52], though the two cases of infant exposure via breastfeeding to a mother on monotherapy revealed neither problematic side effects nor abnormalities in development [51]. Aripiprazole infant serum levels were undetectable at 1 month of age [47, 50]. Given that aripiprazole is a partial dopamine agonist and antagonist, its use may theoretically induce insufficient milk production secondary to reduced prolactin release [47, 48]. Prescribing or continuing aripiprazole during breastfeeding should be done through shared decision-making regarding risk and benefits of the use of this drug for both the mother and the neonate and the possibility of decreased lactation [53].

8.4.6 Amisulpride

Data on infant exposure to amisulpride via breastfeeding is lacking [54]. Two case reports show high transfer of amisulpride into breast milk with maternal dose of 200 mg/day and 400 mg/day, resulting in a relative infant dose of 6.7% to 10.7%,

respectively [44, 55]. These infants, however, experienced no side effects from amisulpride exposure and reportedly had normal development at follow-up. O'Halloran et al. [56] assessed one mother-infant pair with amisulpride exposure in breast milk and found the concentration to be 12-fold higher than simultaneous serum concentration. The infant plasma concentration was about 10.5% of the maternal plasma concentration. Given the lack of quality studies, amisulpride's compatibility with breastfeeding remains largely unknown, and its use in breastfeeding should be evaluated on a case-by-case basis.

8.4.7 Other SGAs and Polytherapy

There has not been a significant amount of data collected on ziprasidone, lurasidone, asenapine, or loxapine. The data available are limited to only a handful of case reports, though no clear pattern of infant adverse effects or negative developmental delays has been noted. Additionally, limited information exists on polytherapy with antipsychotics during breastfeeding. More recently, two instances of breastfed infants exposed to combined antipsychotics have been reported [54]. In one mother-infant pair, the mother utilized olanzapine and haloperidol during pregnancy and continued this treatment while breastfeeding. Through 10 months of age, there were no neonatal side effects or developmental delays. In the other mother-infant pair, the mother exposed the fetus to amisulpride and aripiprazole during the first 4 weeks of gestation, and then after an exacerbation of delusions while off medication, she started haloperidol and amisulpride for the remainder of gestation and throughout 12 months of breastfeeding. No adverse neonatal side effects or developmental delays were noted in the infant at 15 months follow-up.

8.5 Clinical Considerations

Mothers with psychiatric illness are at increased risk for recurrence during the postpartum period, which poses a greater risk of morbidity and mortality to both the mother and the neonate, than exposure to antipsychotics during the lactation period. The exposure of infants to most FGAs and SGAs through breast milk appears to be low and with no significant adverse effects [16, 17]. Therefore, breastfeeding mothers should not necessarily be discouraged from taking an antipsychotic if indicated. In general, patients who have remained stable on a psychotropic regimen during pregnancy should not change medications for the sole purpose of breastfeeding. Preserving postpartum maternal well-being is critical. For patients who are initiating treatment during the postpartum period, medication selection should be guided by what treatment has been efficacious in the past. Given the limited available data on the use of antipsychotics during lactation, a careful risk/benefit assessment as well as close clinical monitoring of the infant for adverse effects is warranted.

While many women often feel considerable societal pressure to breastfeed, nursing may not be the best option in certain circumstances. For example, for women with severe illness, it is also important to consider supporting the decision to forgo breastfeeding. On-demand breastfeeding typically requires breastfeeding every 2–3 h. This sort of feeding schedule can quickly lead to extreme sleep deprivation which may predispose the mother to an increased risk of relapse. Moreover, breastfeeding on a complicated regimen of more than two or three psychotropics at a time is generally not recommended since data on polytherapy and breastfeeding are so limited [54]. Therefore, forgoing breastfeeding may allow the mother to optimize her pharmacologic treatment without worrying about exposing the nursing infant to medications. Bottle-feeding with formula or pumped breast milk (or a combination of both) may also provide maximal flexibility for family and friends to participate in caring for the infant, especially providing assistance with nighttime feedings to help the mother preserve longer periods of uninterrupted sleep.

It is also crucial for the treating psychiatrist and the infant's pediatrician to work collaboratively in supporting the mother's decision to breastfeed or not. Ideally, it is advisable for the mother to discuss her intentions to breastfeed with her psychiatrist and pediatrician prior to delivery. Such a discussion ensures an interdisciplinary team approach that can respond nimbly with any changes in circumstances. In the absence of definitive data on possible adverse effects from antipsychotic exposure through breastmilk, close clinical monitoring of the infant is indicated. Any change in the infant's behavior from his/her baseline with respect to feeding, alertness, sleep, and motor movements should be investigated further. If any acute adverse events are suspected, the mother should immediately suspend breastfeeding which may help to determine whether maternal medications caused the adverse events.

The decision to breastfeed while taking medications is more complicated when a baby is premature or medically compromised [15, 57]. The nursing infant's chances of experiencing toxicity depend on the amount of medication ingested as well as how well the ingested medication is metabolized. Since most psychotropic medications are metabolized by the liver, there is a lower capacity for hepatic drug metabolism (one-third to one-fifth of the adult capacity) during the first few weeks of a full-term infant's life. Over the next few months, however, the capacity for hepatic metabolism increases significantly, and, by about 2–3 months of age, it surpasses that of adults. In premature infants or in infants with signs of compromised hepatic metabolism (e.g., hyperbilirubinemia), breastfeeding typically is deferred because these infants are less able to metabolize drugs and may be more likely to experience adverse events [57].

In addition, measuring drug levels in the breastfeeding baby is not recommended. Data suggest that in most instances, antipsychotic levels are low or non-detectable in infant serum with some exceptions as previously discussed [15, 57]. However, if there is a significant change in the child's behavior (e.g., irritability, sedation, feeding problems, or sleep disturbance), an infant serum drug level may be helpful. If levels are high, breastfeeding may be suspended.

Table 8.1 Expert recommendations based on scientific evidence and clinical experience

Women who are taking an antipsychotic should not be discouraged from breastfeeding. However, sacrificing a mother's mental well-being in favor of breastfeeding is never recommended
The available data, though limited, suggest that the first-generation antipsychotics and second-generation antipsychotics are compatible with breastfeeding with no clear contraindications except for clozapine which is not recommended given the possible risk for agranulocytosis
Collaboratively discuss with psychiatrist, pediatrician, and patient a risk/benefit assessment for breastfeeding on antipsychotics/psychotropics in advance of delivery, and consider factors such as patient preferences, maternal illness history and stability, infant health status, and maternal sleep deprivation/disruption
Polytherapy, i.e., co-administration of more than one antipsychotic and/or complex psychotropic regimen (>2 psychotropics), is generally not recommended during lactation due to limited safety data using a combination of medications
Infants exposed to an antipsychotic through breast milk should be carefully monitored for adverse events including any changes in infant behavior, alertness, feeding, or sleep

8.6 Conclusion

In summary, women who are taking an antipsychotic should not be discouraged from breastfeeding. The overwhelming evidence, although limited, suggests that most FGAs and SGAs appear to be compatible with breastfeeding. The only exception may be clozaril given its potential risk of seizure and agranulocytosis in the exposed nursing infants. Under certain clinical circumstances, however, mothers with serious mood and/or anxiety disorders should be counseled not to breastfeed, given the physical demands on the mother, especially with respect to sleep deprivation which is a strong predictor of relapse. In the absence of definitive data on adverse effects from antipsychotic exposure through breast milk, close clinical monitoring of the infant is indicated.

Clinical decisions regarding breastfeeding and antipsychotics or other psychotropics should be based on a careful assessment of risks and benefits to both the mother and infant, bearing in mind the serious detrimental effects of untreated mental illness and the many health and emotional benefits of breastfeeding. Sacrificing a mother's mental well-being in favor of breastfeeding is never recommended. With the recent overhaul of the FDA's pregnancy risk category labeling system in favor of the Pregnancy and Lactation Labeling Rule [58], we anticipate further research and progress on the safety of medications during lactation. Indeed, more robust data are needed in order for healthcare providers and their patients to engage in well-informed, collaborative decision-making (Table 8.1).

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Mood Stabilizers in Pregnancy

9

Anne-Laure Sutter-Dallay and Florence Gressier

9.1 Introduction

Seven percent of women presenting a bipolar disorder had their first episode in the context of the perinatal period [1]. In women with bipolar disorder prior to pregnancy, the risk of relapse may reach up to 20% during pregnancy [2] and is between 50% and 70% postpartum [1, 3]. Conversely, bipolar disorders themselves seem to have a possible influence on the course of pregnancy, as a study [4] shows that the risk of obstetric complications is higher in bipolar patients, treated or not, than in the general population. Thus, working in a preventive perspective during this period of a woman's life is crucial. The specificities of pregnancy in women of childbearing age suffering from bipolar disorders should be addressed in the gynaecological or psychiatric care. If no pregnancy is planned, methods of contraception should be reviewed with the patient, as certain anticonvulsive mood stabilizers are strong enzyme inducers that reduce the efficacy of oral contraceptives or progestogen-releasing implants (e.g. carbamazepine, oxcarbazepine and topiramate) [5]. Conversely, oral contraceptives combining ethinyloestradiol/levonorgestrel increase lamotrigine clearance [6, 7]. Women should also be informed of the impact of these

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treatments on their fertility, particularly with regard to valproate, which are likely to be associated with elevated levels of testosterone and hyperandrogenism in women with bipolar disorders [8]. Furthermore, women should be educated about the risk of unwanted pregnancy when stopping hyperprolactinaemia-inducing antipsychotics, when used as mood stabilizers. The ethical dimension of the benefit/risk management of each pregnancy is thus evident and faced with a pregnancy involving mood stabilizers; the patient first needs reassurance, because the stress caused by worrisome information can in itself lead to a relapse, especially in the case of bipolar disorders.

Data regarding mood stabilizers during pregnancy remain poor, are quite always retrospective and frequently carried out on small-size samples [9]. In addition, the main part of the researches does not take into account the influence of maternal somatic disorders on foetal development and pregnancy on issues such as malnutrition, obesity, diabetes and gynaecological infections nor the influence of environmental factors such as an unhealthy lifestyle or domestic violence. Keeping these general limitations in mind, a summarization of the current literature allows defining a general prescription framework.

9.2 Lithium

9.2.1 Placental Transfer

Newport et al. [10] by combining the results of a prospective sample of 10 women with 32 cases of neonatal dosages identified in the literature suggest that placental transfer of lithium is complete and that the balance between maternal and foetal circulation (average child/mother plasma lithium ratio = 1.05 ratio) is between the different fluid compartments of an individual. Another study [2] found neonatal blood lithium levels above 0.8 mEq/L in 2 of the 30 exposed children, one of which presented signs of neonatal distress. This work does not provide blood levels of the other children included in the sample, and neither of the two took into account co-prescriptions of other psychotropic drugs.

9.2.2 Embryonic Period: Organogenesis

The first studies on lithium teratogenicity are animal studies dating from the end of the nineteenth century [11]. In animals exposed antenatally to doses used for treatment in human beings, no increase in teratogenic risk has been noticed. With very high doses, some studies reveal different types of malformations (central nervous system, skeletal, craniofacial, etc.), while others did not find any link between prenatal exposure to lithium and birth defects [11]. The first data on lithium's teratogenicity in humans are issued from the "Register of Lithium Babies", which collected retrospectively the pregnancy outcomes of patients treated by lithium in Scandinavia, the United States and Canada. The first publication reported 118 cases of

Scandinavian children whose mothers had taken lithium during the first trimester of pregnancy [12]. Nine of them (7.6%) presented birth defects, among which six were related to the cardiovascular system, including one Ebstein's anomaly (severe malformation of the tricuspid valve). By adding other data from the United States and Canada, the number of cases reported increased to 143. In this second sample, cardiovascular malformations accounted for 77% of congenital defects, against 12.5% in the general population. Ebstein's anomaly was largely over-represented: 40% of babies from the registry against 1.25% of cardiac malformations in the general population. The final publication [13] included 225 observations (at least three children were also exposed to other treatments), among which 11% ($n = 25$) of the children presented congenital malformations (2% in the general population). Three-quarters of these malformations were cardiovascular ($n = 18$), while 33% ($n = 6$) were Ebstein's anomalies. The retrospective collection of data in this register represents a major bias, since it is likely that pathological cases have been more frequently reported than normal births. Subsequent retrospective studies used more strict data collection methods and did not reveal statistically significant relation between the use of lithium during pregnancy and the occurrence of cardiac malformations in the newborn nor specific links between Ebstein's anomaly and prenatal exposure to lithium [14, 15]. The recent study from Patorno et al. [16], revealing an adjusted risk ratio for cardiac malformations among infants exposed to lithium as compared with unexposed infants of 1.65, also underlines that the risk ratio was 1.11 for a daily dose of 600 mg or less, 1.60 for 601–900 mg and 3.22 for more than 900 mg.

On the other hand, a review of 59 cases of Ebstein's diseases found no cases of children exposed to lithium in early pregnancy [17]. Boyle et al. [18], in a study describing the epidemiology of Ebstein's anomaly in Europe and its association with maternal health and medication exposure during pregnancy through population-based data, reported that cases exposed to maternal mental health conditions/medications had an increased adjusted odds ratio risk of 2.64 compared with cardiac controls rather than lithium. Authors underlined therefore that changing or stopping medications may not be preventative.

Prospective studies remain rare [19], sometimes unpublished [20], and mainly do not show a statistically significant link with birth defects, although some note the existence of sporadic cases of Ebstein's anomaly [19, 20]. A recent prospective, comparative observational study [21] followed up 183 lithium-exposed pregnancies of women who contacted the Israeli Teratology Information Service (90.2% in the first trimester) and were compared with 72 disease-matched and 748 nonteratogenic-exposed pregnancies. The rate of major congenital anomalies was not significantly different between the groups (lithium-exposed in the first trimester, 8/123 [6.5%]; bipolar, 2/61 [3.3%]; nonteratogenic, 19/711 [2.7%]). Cardiovascular anomalies occurred more frequently in the lithium group exposed during the first trimester when compared with the nonteratogenic exposure group (5/123 [4.1%] compared with 4/711 [0.6%]) but not after excluding anomalies that spontaneously resolved (3/123 [2.4%] compared with 2/711 [0.3%]).

Case-control studies have failed to demonstrate a significant association between birth defects and in utero exposure to lithium [17, 20] when case reports in the

literature indicate both heart defects, sometimes with Ebstein's anomaly, and other types of defects, including neural tube defects [20].

Finally, a meta-analysis [22] about general toxicity of lithium concluded that the risk of congenital malformation after early in utero exposure to lithium is "uncertain" and that the benefit/risk balance of a decrease or a discontinuation of treatment during pregnancy should be weighed for each clinical situation. Facing a probably slight increased risk of heart defects in this population, it is therefore recommended that all women receiving lithium during pregnancy should undergo foetal echocardiography and a level 2 (anatomic scan) ultrasound examination between 18 and 20 weeks of gestation [23].

9.2.3 Foetal and Neonatal Periods

Lithium use during the foetal period is likely to lead to a significant increase in birth weight [21]. Paediatricians should carefully monitor babies during the first 48 h for foetal goitre, hypotonia, bradycardia, arrhythmias, systolic murmur, hypothermia, cyanosis, tachypnoea and poor sucking reflex [10], although all reports describe full recovery of the infants [24]. The recommendation is therefore to refer these patients to maternity hospitals with neonatal paediatric resources.

9.2.4 Child Development

The question of an effect on foetal brain development in the long term remains as brain structures develop throughout pregnancy and may be particularly susceptible to the impact of psychotropic drugs. Currently, the extreme paucity of data does not allow any conclusions. An animal study reported long-term effects with "anxious" persistent behaviour in pups of dams treated [25]. Results at 5 [12] and 15 years of age [2] suggest no distinctive features of these babies as they mature. A very recent study on the topic [26] exploring a small clinical cohort showed no significant association between mothers' prenatal exposure to lithium or mood disorders and offspring's IQ. In a systematic review, Haskey and Galbally [27] concluded that the existing data on lithium are reassuring, but are of limited quality, indicating that further research is required.

9.2.5 Maternal Complications

The increase in the distribution volume and in renal excretion rates among pregnant women usually leads to an increase of doses during pregnancy, to maintain blood levels as low as possible within the therapeutic range. A recent study provided the kinetics of lithium blood levels during the course of pregnancy: decreased in the first trimester (−24%), reached a nadir in the second trimester (−36%), increased in the third trimester (−21%) and still slightly increased postpartum (+9%) [28].

Given these variations, it is recommended to perform serum assays every 4 weeks up to 36 weeks of gestation and then weekly until birth [29]. After birth, the decline of distribution volume will lead to a decrease in doses because of the risk of overdosage. Thereafter, requirements will be adapted according to standard protocols while maintaining special vigilance in the first 15 days postpartum. Note that some authors [10] propose to achieve a therapeutic window in 24–48 h before delivery when scheduled, or upon start of delivery, with reintroduction immediately after birth.

9.3 What to Do

Lithium is no longer really contraindicated during the first trimester of pregnancy and is certainly not in itself an indication for termination of pregnancy today. The risk of birth defects must also be considered in the light of the availability of ultrasound screening and the progress in paediatric cardiac surgery. Here, even more than with other psychotropic drugs, assessing the benefit/risk ratio for each patient is essential. Viguera et al. [30, 31] have emphasized the importance of mood stabilization during pregnancy when necessary: women who stop their lithium treatment during pregnancy have a risk of postnatal recurrence twice as high as non-pregnant patients, and this recurrence may occur four times more rapidly and last five times longer. If the choice is to stop treatment, discontinuation must be progressive, even if the embryo is exposed, because the teratogenic risk is currently considered to be less than that of decompensation generated by abrupt cessation [32]. If treatment is continued throughout the pregnancy, the marked variation in blood volume and the increased rate of renal excretion during pregnancy make regular monitoring of maternal plasma and erythrocyte levels of lithium necessary. Progressive decrease in dose in the days preceding birth can be proposed to avoid an overdose in the immediate postpartum period. Proper hydration must be maintained during labour to avoid neonatal overdosing. In the postpartum, regular assays of plasma and erythrocyte lithium should be performed and dosage adjusted until the appropriate balance is obtained.

9.4 Antiepileptic Drugs

9.4.1 Placental Transfer

The only work of Bank et al. [33] found mean umbilical-to-maternal ratios for total concentrations ranging from 0.79 for carbamazepine to 1.20 for valproic acid and mean umbilical-to-maternal ratios for free concentrations ranging from 0.86 for valproic acid to 1.42 for carbamazepine, indicating complete placental passage. However in this study, neither umbilical cord concentrations nor umbilical-to-maternal ratios were associated with adverse neonatal outcomes.

9.4.2 Carbamazepine

9.4.2.1 Embryonic Period: Organogenesis

Data about the use of carbamazepine during pregnancy mainly concern women with epilepsy; reports about women with psychiatric disorders are extremely rare, although this antiepileptic drug is indicated for bipolar disorder. Either the Food and Drug Administration (FDA) or the European Medicine Agency (EMA) does not contraindicate it for use during pregnancy for epileptic patients. Nevertheless, studies have reported an increased risk of spina bifida in children exposed during the first trimester [5, 34] and a possible dose effect on global major congenital malformation rates [35]. Nonetheless, a recent large population-based study found antenatal exposure to carbamazepine had no effect on this risk [36].

9.4.2.2 Foetus Neonate and Child Development

Increased risks of small head circumference and low birth weight for gestational age have been reported [34, 36]. The enzyme-inducing effect of carbamazepine must also be considered in neonatal care of the baby. Most studies of its effect on child cognitive development report a slight impact, specifically on verbal abilities [37, 38].

9.4.2.3 What to Do

The risk of congenital malformations necessitates supplementation with folic acid for 2 months before and after conception to prevent neural tube defects [39].

Ultrasound monitoring is recommended along with an assay of maternal serum levels of alpha-fetoprotein before the 18th week of gestation [34]. Lastly, regular care and monitoring in a neonatal paediatric department is recommended for the child.

9.4.3 Valproates

9.4.3.1 Embryonic Period: Organogenesis

The prescription of valproates is contraindicated during the first trimester of pregnancy. The teratogenic risk is significant, with a global malformation rate around 10% (four times higher than with other antiepileptic drugs), mainly of the central nervous system (1–2% compared to 0.1% in the general population) [5, 34, 40]. In cases of exposure in early pregnancy, some authors consider that the risk of teratogenesis outweighs that of mood decompensation and advocate rapid cessation. Specific ultrasound to screen for malformations is required as early as possible, and abortion counselling must be offered if they are suspected.

9.4.3.2 Foetus and Neonate

Valproate may lead to a haemorrhagic syndrome in the newborn, although its cause is still unclear (possibly a combination of impaired platelet aggregation, thrombocytopoenia and decreased fibrinogen). Monitoring of haemostasis is thus required in

the mother before delivery and in the neonate at birth. The baby also appears to be at risk of hepatocellular insufficiency. Some studies have described a risk of neonatal hypoglycaemia [34]. Another important concern is the risk of impaired cognitive development in infants of mothers treated with valproates [27, 41]. The EMA recently issued a warning against prescribing these drugs to women and girls of childbearing age (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f). The French national agency of medications recently banned the prescription of valproates in women of childbearing age [42].

9.4.3.3 What to Do

In view of the clear increase in the risk of congenital malformations caused by the use of valproates during pregnancy, supplementation with folic acid from 2 months before to 2 months after conception is essential to prevent neural tube defects [39].

Monitoring by special ultrasonography is strongly recommended, together with an assay of maternal serum levels of alpha-fetoprotein before the 18th week of gestation. During pregnancy and after childbirth, maternal and child coagulation and hepatic functions and maternal blood concentrations of valproate should all be monitored regularly.

9.4.3.4 Lamotrigine, Topiramate and Gabapentin

Lamotrigine is not contraindicated during pregnancy [43]. However, it may cause defective organ development, with a possible dose-effect relation with cleft palate, not yet confirmed [35]. A recent review concluded that "it is not clear that foetuses of lamotrigine-exposed pregnant women are at higher risk of malformation or neurodevelopmental delay" [44]. Recently, lamotrigine was found as not being inferior to lithium in the prevention of severe postpartum episodes, suggesting that lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum [45].

Topiramate was found associated with a significantly increased risk of oral cleft in infants, possibly dose related [46, 47]. No consistent data are available regarding gabapentin.

9.5 Conclusion

One of the most important specificities of the perinatal period is the real possibility of preventive care that protects against harm to both mother and child. Psychiatrists must always bear in mind the importance of discussing pregnancy plans with women of childbearing age suffering of a bipolar disorder, preferably before they become pregnant.

If pregnancy occurs, regular follow-up by a specialist team should be offered whenever possible. Management must be nested in a multidisciplinary network to anticipate specific postnatal care such as extension of the maternity stay, home help,

Table 9.1 Expert recommendations based on scientific evidence and clinical experience

Regarding the increased risk of bipolar disorder episodes during pregnancy, clinicians have to be able to prescribe after weighing the risks of a maternal relapse vs. the risks of antenatal exposure to the drug
The available limited data suggest that there is no contraindication regarding the use of lamotrigine at doses less than 350 mg/day during pregnancy (increased risk of oral cleft with higher doses)
The available limited data suggest that there is no longer absolute contraindication regarding the use of lithium during the first trimester of pregnancy
Valproate must be avoided during all the pregnancy because of the increased risk of defects and developmental disorders for the child
Carbamazepine may increase birth defects and impact some developmental axes
Bipolar women must be treated during pregnancy, to avoid risk-taking behaviour and deterioration in the prognosis of the disorder over the long term as well as the risks for the foetus of the effects of prenatal stress, increased smoking or poor nutritional intake

community-based intervention or any other type of specific care provided for by local or national perinatal mental health policies. Given the complexity of management, the psychiatrist must ensure close interdisciplinary care, if possible in the form of a liaison and consultation service; it is especially important that all involved are aware of the effects of medications on the mother, the embryo and the foetus, including the effects that differ according to gestational age (Table 9.1).

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Mood Stabilizers During Lactation

10

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10.1 Introduction

Bipolar disorder usually starts in the late teens and early twenties, and because of this, women suffering from this ailment remain at risk of an episode throughout their reproductive life [1]. Further, available data suggests that most of the affective disorders, which are postpartum in onset, usually turn out to be bipolar disorder in the longitudinal course [2].

Mood stabilizers (MS) form an integral part of the management of bipolar disorders. Due to the severity of the illness, many women are continued on MS during pregnancy, which are carried through into the postpartum period. MS are also often started in the immediate postpartum period in women in whom these medications were withheld during the pregnancy or at the time of delivery. These medications are also often considered for postpartum-onset bipolar disorders. Continuation or discontinuation of MS during pregnancy and lactation requires appropriate knowledge about the risks and benefits of these medications, both for the mother and the baby [3]. In this chapter, we discuss the risks and benefits of the use of MS during the postpartum period, both for the mother and the newborn.

In general, the conventional MS include lithium, sodium valproate and its congeners, lamotrigine and carbamazepine. In recent times, other antiepileptic agents like gabapentin and atypical antipsychotics like aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, etc. have also been considered to have mood-stabilizing properties [4]. Medications like clonazepam, calcium channel blockers, etc. have also been evaluated as MS. In this chapter, we would mainly focus on the conventional agents, as information on other agents is presented in other chapters. Issues related to use of MS during pregnancy and delivery are not addressed in this chapter.

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10.2 Risk of Relapse of Bipolar Disorder During Pregnancy and Postpartum

Available data suggests that there is high risk of relapse during pregnancy [5–7] and the early postpartum period [8–10]. Also the risk of relapse during pregnancy has been estimated to be 50% or more [5–7], with 2.3 times higher risk of recurrence on discontinuation of MS. A prospective study showed that compared to women who continued the MS during the pregnancy, those who stopped the MS during pregnancy spent about five times longer duration (8.8% versus 40%) of their pregnancy, in the episode [7]. Risk of episodes during the postpartum period has been estimated to be 40–70% higher among untreated bipolar women [11], and the risk is higher in those who discontinue prophylactic treatment [10]. Among the various risk factors for relapse, the rate of discontinuation of MS has been found to be an important marker, with higher risk of relapse associated with rapid discontinuation of MS [7]. Considering these facts, selection of appropriate MS for women of reproductive age group, especially during pregnancy and postpartum, requires weighing all the pros and cons of the use of these drugs. The treating clinicians often face the challenge of minimizing the risk to the foetus along with minimizing the impact of maternal morbidity. Clinicians often have to consider either to use or not to use MS and determine the reasonable risk with both strategies. It is suggested that considering something as a reasonable risk during pregnancy involves shared responsibility between the patient and the treating clinician, but it is important to remember that the final decision about treatment lies with the informed patient.

10.3 Beneficial Effects of Breastfeeding

Postpartum period is associated with the additional clinical dilemma of lactation and breastfeeding. The beneficial effect of breastfeeding for both infant and mother cannot be underscored. Breast milk is considered as an ideal form of nutrition, which confers many advantages to the newborn. As per the American Academy of Pediatrics, besides being an important contributor to the establishment of emotional bond and attachment between the mother and the infant [12], breast milk is known to reduce the incidence and/or severity of a wide range of infectious diseases [13], postneonatal-infant mortality rates, sudden infant death syndrome in the first year of life, incidence of insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetes mellitus, haematological malignancies (i.e. lymphoma, leukaemia, Hodgkin disease), overweight and obesity, hypercholesterolaemia and asthma in older children and adults [12]. Breastfeeding has also been reported to be associated with slightly better performance on tests of cognitive development [14]. In terms of maternal benefits, breastfeeding has been reported to decrease postpartum bleeding, leads to faster uterine involution, decreased menstrual blood loss, child spacing by lactational amenorrhoea, earlier return to pre-pregnancy weight, reduction in the risk of breast and ovarian cancer and possibly decreased risk of hip fractures and osteoporosis in the postmenopausal period [15]. Considering these benefits, in

general, breastfeeding is recommended for all newborns, with very few absolute contraindications. Use of medications and drug use are considered as relative contraindications for breastfeeding [16].

Accordingly, continuing or discontinuing breastfeeding while continuing MS is often associated with an ethical dilemma and difficult decision-making. The risk-benefit should be evaluated by taking physiological and psychological benefits of breastfeeding into consideration, the potential negative impact of untreated maternal mental illness on the infant, maternal-child bonding, negative consequences of MS on the cognitive and behavioural development of the newborn, and the consequences of untreated mental illness on the mother [17]. In general, all efforts must be made to continue breastfeeding while minimizing the negative consequences of use of MS and other psychotropics. This requires some understanding of physiology of the breast milk secretion.

10.4 Understanding the Physiological Aspects of Breast Milk Secretion and Use of Mood Stabilizers During Lactation

Breast milk secretion can be broadly understood as foremilk and hindmilk. Foremilk is expressed during the first half of a feed and has lower lipid content, whereas hindmilk, which is secreted during the second half of a feed, is rich in lipid content. Due to higher lipid content, hindmilk contains higher quantity of lipid-soluble psychotropic medications compared to the milk secreted in the first half [17]. Additionally, the exposure of the newborn to medications is influenced by the rate of absorption of medications into the maternal circulation, diffusion of medications from maternal circulation to the breast milk and absorption of the medications in the infant. It is important to understand that the concentration of a medication in breast milk depends on the nonprotein-bound concentration of the drug in maternal plasma. Accordingly, the factors that are taken into account to determine the concentration of the medication in breast milk, plasma protein binding, volume of distribution, lipid solubility, molecular weight and p*K*a-pH. Medications which have high plasma protein binding will have low secretion in breast milk, for example, selective serotonin reuptake inhibitors (SSRIs) have high plasma protein binding, whereas venlafaxine has low plasma protein binding. Accordingly, the concentration of venlafaxine is expected to be more than the SSRIs. Medications which have large volume of distribution will get sequestered in different fluid compartments leading to low maternal plasma levels and thus have low levels in breast milk. Medications which have high lipid solubility, such as majority of the psychotropic medications, easily pass through the alveolar cells and thus have more secretion into breast milk. Drugs with higher molecular weight have slower diffusion rate and slower transfer into the breast milk. The p*K*a-pH value of a particular drug is that pH at which the medication is equally ionic and nonionic. Ion trapping occurs when p*K*a is more than 7.2, leading to high concentrations in breast milk [18].

In clinical and research practice, the relative infant dose is an estimate of the amount of drug dose of the breastfeeding infant. Usually, milk to plasma ratio is considered an indicator of the secretion of the medication in the breast milk. The

relative infant dose is calculated as dose in infant in mg/kg/day/dose in mother in mg/kg/day. Dose in infant is the concentration of the medication in the breast milk divided by the volume of breast milk consumed daily. Practically a relative infant dose of <10% is considered as acceptable, whereas drugs having a relative infant dose >25% are considered to have therapeutic effect if absorbed and are accordingly unacceptable [18]. However, it is important to remember that absorption of medication also depends on the oral bioavailability in the infant. Limited data is available on the oral bioavailability of drugs in infants. In addition, inadequate information is available regarding how much infant plasma concentration has the potential to harm [3].

Factors which influence the quantity of medications in the breast milk include serum albumin, lactose, lysozyme and other enzymes, prolactin levels and minerals like calcium and phosphates [17]. It is also important to understand the factors which influence the excretion of various medications from the body of the neonates. Neonatal cytochrome P-450 activity is about half of that seen in adults. Most of the neonates take about 2 weeks' time to develop, from minimal levels to almost adult levels, the capability to conjugate various compounds [19]. The kidneys of the neonates are also functionally immature; hence, various medications which are primarily eliminated through the kidney tend to accumulate. Effects of various medications on the brain also depend on the blood-brain barrier (BBB), and it is well known that, compared to adults, the BBB in neonates is also immature, which leads to higher concentration of lipid-soluble agents (10–30 times) in the CSF than in serum. Additionally, compared to older infants, fat storage sites are relatively lower in the neonates. This leads to higher concentration of lipid-soluble substance in the central nervous system of newborns [17]. Accordingly, all these facts must be considered while recommending breastfeeding in a newborn.

10.5 MS and Lactation

10.5.1 Lithium

There is limited data in terms of the effect of continuation of lithium during the postpartum period and continuation of breastfeeding. Studies have estimated the serum lithium levels in infants, whose mothers having been taking lithium in the dose of 600–1500 mg/day during breastfeeding, and these have reported the levels among neonates to vary from 0% to 30% of the maternal levels [20, 21]. However, a recent case report estimated infant serum lithium levels to be 58% of the maternal levels [22]. Another study evaluated the maternal level, levels of lithium in breast milk and levels in the infants of ten mothers taking lithium in the dose of 600–1200 mg/day. The maternal levels varied from 0.43 to 1.31 mmol/L, the levels in the breast milk were found to be 0.19–0.48 mmol/L and infant levels were found to be 0.08–0.25 mmol/L [23]. In terms of neonatal side effects, occasional reports have documented adverse effects like hypothermia, hypotonia, lethargy and T wave

modifications on electrocardiogram (ECG) among neonates whose mothers were taking lithium during the postpartum period. There is some data to suggest possible association of feeding difficulties with maternal use of lithium during postpartum, but the evidence for this is inconclusive [20].

10.5.2 Valproate

Available data suggest that valproate is minimally secreted in breast milk. A small sample size study, which estimated the valproate level in six breastfed mother-infant pairs, reported infant serum valproate levels in the range of 0.9–2.3% of the mother's serum level [24]. Another study, which was limited to two infants whose breastfeeding mothers were taking valproate, reported valproate levels in the infants to be 1.5% and 6%, respectively [25]. The American Academy of Neurology (AAN) and American Academy of Pediatrics (AAP) support breastfeeding if the mother is taking valproate [26, 27]. However, it is important to remember that there are occasional case reports that have documented side effects in the form of anaemia, reticulocytosis and thrombocytopenic purpura in the infants, whose mother was treated with valproic acid during the postpartum period. These side effects disappeared when the mother stopped breastfeeding [28].

10.5.3 Carbamazepine

Most of the data on carbamazepine in breastfeeding infants have been based on the assessment of offspring of mothers who took the drug during pregnancy. The concentration of carbamazepine has been estimated to be 6–65% of maternal levels among neonates [29]. However, it is important to note that there are occasional case reports of transient hepatic dysfunction [30, 31] in infants, whose mother was taking carbamazepine during the breastfeeding [30, 31]. The neonate developed transient cholestasis with pale stools and marked elevations of glutamyltransferase (322 U/L), conjugated bilirubin (3.5 mg/dL), bile acids (78.5 μg/mL) and raised transaminase levels (AST 112 U/L, ALT 56 U/L) with normal coagulation profile between the third and seventh week of life [30]. Both AAN and AAP support breastfeeding if the mother is taking carbamazepine [26, 27].

10.5.4 Oxcarbazepine

Oxcarbazepine, a congener of carbamazepine, has been used for the treatment of bipolar disorders. There is lack of data on the use of oxcarbazepine during the breastfeeding. A case report suggests a low milk/plasma ratio (0.5) and a low concentration in human milk (<11 μg/mL) with a low relative infant dose (1.5–1.7%) [32].

10.5.5 Lamotrigine

Available data in the form of case reports and case series suggest mean milk/plasma ratios for lamotrigine to range from 0.40 to 0.61 [33–36]. A study which involved 30 breastfeeding mothers receiving lamotrigine (50–800 mg/day; mean = 386.5) and their infants reported a mean milk/plasma ratio of 41.3% with a range of 5.7–147%. Lamotrigine concentrations were higher in the breast milk 4 h after the intake of the drug by the nursing mother, although the finding was not statistically significant. Infant plasma concentrations were 18.3% of that reported for nursing mothers. However, except for mild thrombocytosis in seven out of eight infants, no other adverse events were observed [37]. A recent case report documented multiple episodes of apnoea in the newborn while the mother was receiving lamotrigine, which improved completely when the breastfeeding was terminated [38]. LactMed considers use of lamotrigine during breastfeeding to be relatively safe and recommends to evaluate the plasma levels and to monitor the platelet count of infants.

10.5.6 Topiramate

A small sample study involving five mother-infant pairs reported very low topiramate concentrations in the infants, with no adverse effects seen among the infants [39]. Mean milk/maternal plasma concentration ratio was 0.86 (range, 0.67–1.1) at 2–3 weeks and 1 month and 0.69 at 3 months after delivery. Two out of the three infants who were breastfed had detectable topiramate levels, i.e. >0.9 μmicroM concentrations; however, this was lower than the limit of quantification (2.8 microM), and one infant had an undetectable concentration [39]. There are other case reports of safe use of topiramate during lactation [40]. However, a recent case report documented the association of diarrhoea with topiramate while breastfed by a mother who was receiving topiramate [41].

10.5.7 Gabapentin

The mean milk/maternal plasma concentration ratio of gabapentin in milk has been estimated to be 1.0 (range, 0.7–1.3) from 2 weeks to 3 months. Accordingly, the mean infant dose is reported to be 0.2–1.3 mg/kg/day, which is much lower (1.3–3.8%) of the maternal dose. In terms of plasma concentrations, plasma concentration in breastfed infants has been estimated to be 12% of the mother's plasma levels. No adverse effects were observed with low plasma concentration in the breastfed infants [42]. In a case report, the relative infant dose was estimated to be 2.34%, with absolute infant dose being approximately 3% of the recommended children's dose for gabapentin, and the infant plasma level was 0.4 mg/L, which was about 6% of the maternal plasma drug concentration. No adverse events were reported in the infant [43].

10.6 Recommendations for Use of MS During Puerperium and Lactation

Table 10.1 summarizes expert recommendations on the use of MS during the lactation period. There is high risk of relapse among patients with bipolar disorder during the puerperium. Hence, reinitiating the MS in the immediate postpartum period is recommended for patients at high risk of relapse. Available data suggests that use of lithium as a prophylactic agent in the postpartum period brings down the relapse rate from nearly 50% to less than 10% [44].

Starting a MS during the postpartum period for the first episode of hypomania/mania/mixed episode is a tricky one, and this must be based on the consideration of severity of symptoms and risk of continuation of symptoms to the mother and the foetus, including mother-child bonding. If the symptoms are severe enough, use of MS needs to be considered.

If the MS is started, then the risk and benefits of whether to allow breastfeeding or not should be taken into account. The risk-benefit analysis should take into consideration the benefits of breastfeeding (both physiological and psychological), the desires of the mother, the risk of infant exposure to the medication and the possibility of refusal to treatment by a severely ill mother in favour of giving up breastfeeding [15].

If the decision is made to continue the breastfeeding while using MS, the newborn should be evaluated at the baseline and also must be monitored closely to minimize the risk. The newborn should be examined by a paediatrician for baseline behaviour and other parameters like sleep, feeding and alertness. The newborn should be then evaluated from time to time by the paediatrician to ensure normal development. The parents need to be informed about the possible side effects with the medication being used.

Certain physiological changes which occur during the infancy must be remembered, which can help in minimizing the negative effects of the MS on the infant, who is continued on the breastfeeding. Older infants metabolize and eliminate various drugs more efficiently than the younger infants, and they generally sleep for longer durations. The long duration of sleep can help in planning the dosing of the

Table 10.1 Expert recommendations based on scientific evidence and clinical experience

• High risk of relapse in the postpartum period
• Initiation and continuation of mood stabilizer must be considered
• Decision to breastfeed the newborn must consider the risks and benefits
• Baseline and regular evaluation of the newborn by a paediatrician is a must, with close monitoring for side effects
• Lowest effective dose of mood stabilizer should be used
• Medications must be timed according to the neonates' feeding pattern
• Valproate is considered safe; monitoring of infant LFTs recommended
• Breastfeeding should be done with caution in mothers receiving lithium; regular monitoring of ECG, lithium levels and blood counts to be done; information to be given to parents regarding warning signs in the newborn
• Lamotrigine is considered safe; however, data is sparse
• Carbamazepine may be used with caution and monitoring

mother. It is generally recommended to administer the dose to the mother immediately after breastfeeding and just prior to the baby's longest sleep interval [3]. While allowing breastfeeding, a close liaison needs to be maintained with the paediatrician, and the discussions need to include sharing information about potential side effects of medication exposure to the newborn and possible drug interactions with other commonly prescribed medications to infants (e.g. antibiotics, nonsteroidal anti-inflammatory agents, acetaminophen).

If the MS is used during the breastfeeding, the dose must be kept at the lowest effective dose. However, such an attempt must not lead to ineffective dosing, poor symptom control and resultantly unnecessary exposure to the neonate.

In terms of selection of the MS, valproate is considered to be safer than lithium. The AAN and AAP support breastfeeding if the mother is taking valproate [26, 27]. However, monitoring of liver function tests and blood counts for the newborn is recommended. Accordingly, if a clinician needs to start MS for the first time during the postpartum period and the parents/mother wishes to continue breastfeeding, valproate needs to be considered as the preferred agent.

According to the recommendations of AAP, breastfeeding should be done with caution while using lithium in mothers, and if this is permitted, then the breastfed infant needs to be monitored for serum lithium levels, ECG and complete blood counts from time to time [27]. Accordingly, lithium needs to be used, when this has been used during pregnancy or the patient has past history of response to lithium. If there are no contraindications, the mother may be given an option to switch to valproate. It is important to remember that mothers may require lower doses of lithium during the postpartum period, when compared to those required during pregnancy. Hence, the maternal lithium dose needs to be reduced to the pre-pregnancy level, immediately after delivery, and serum lithium levels must be monitored. Further, the mother must be informed to monitor the newborn for signs of dehydration, lethargy and feeding problems. The newborn must be screened for thyroid and renal functions, and maternal and infant serum lithium levels must be done if clinically indicated. The renal functions of the newborn must be monitored closely, especially during the first 6 weeks of life. The newborn must also be monitored for subtle neurological signs and needs to be referred for early intervention when indicated [7].

Lamotrigine is also considered safe during breastfeeding. However, it should be used during lactation when other safer options are not available. If carbamazepine is used, then the infant should be monitored closely for jaundice, drowsiness, adequate weight gain and developmental milestones [45]. LactMed database also recommends similar monitoring of breastfeeding infants, whose mother is receiving carbamazepine. Data for other anticonvulsants is cursory.

10.7 Conclusion

The issue of safety of use of MS during lactation is far from being resolved. Accordingly, the decision to prescribe while continuing breastfeeding should be taken in the light of severity of mental disease, and MS should be considered only

when the potential risk to the foetus from exposure to medication outweighs the risk of untreated maternal mental disorder. The selection of the medication depends on the balance between safety and efficacy profile. Whenever MS are started during lactation, the newborn must be monitored closely.

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Benzodiazepines and Z-Drugs in Pregnancy

11

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11.1 Introduction

Benzodiazepines (BZDs), together with the so-called Z-drugs, represent one of the most widely used psychotropic drugs prescribed, not only in psychiatric practice but also in several medical fields, for the treatment of several psychopathological conditions. It has been estimated that 5–15% of adult general population receives a prescription of such drugs, particularly amongst women, and for longer periods of time [1, 2].

It has also been documented that approximately 50% of adults report a difficulty in initiating or maintaining sleep or having unrefreshing sleep (i.e. symptoms of insomnia), whereas upwards of 20% of adults meet strict diagnostic criteria for clinically relevant insomnia [3].

During the last two decades, with a parallel increased focus in the clinical research and development of newer antidepressants and antipsychotics, we assisted to a reduced interest in BZDs, therefore, generating the *false impression* that these drugs represent an outdated issue in the field of clinical psychopharmacology, despite their current widespread use in the general population [4].

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Currently, BZDs and Z-drugs are routinely prescribed in the treatment of many psychopathological conditions, including the treatment of anxiety symptoms, sleep disorders and as add-on therapy for schizophrenia and other psychotic disorders. On the other hand, it has been well known that prescribing anxiolytic and sleep-promoting drugs may be responsible for their uncontrolled, long-term and not evidence-based use, with a higher potential for abuse, misuse and dependence, particularly amongst the polydrug abusers [5–7].

However, it should be underlined that the above risks need to be always carefully balanced with the clinical benefits that many patients may experience with a short or intermittent use of these drugs. Considering the current widespread consumption of these agents, both in general practice and in specialist psychiatric and nonpsychiatric setting, it would be very desirable, for a more appropriate use, to encourage the implementation of specific training interventions concerning the BZD and Z-drug use, in order to minimize both the risk of abuse and/or misuse by patients and the risk of malpractice by prescriber.

11.2 Pharmacology of Benzodiazepines and Z-Drugs

Benzodiazepines (*BZDs*) comprise a pharmacological class of psychodrugs including agents that work on the central nervous system, by selectively acting on gamma-aminobutyric acid alpha-receptors (GABA-$_A$) in the brain. GABA is a neurotransmitter that inhibits or reduces the activity of neurons within the brain, particularly in the amygdala and prefrontal cortex. BZDs open GABA-activated chloride channels and allow chloride ions to enter the neurons. This makes the neuron negatively charged and resistant to excitation. BZDs work in a similar way, but there are differences in the way in which a specific BZD acts on the different GABA-$_A$ receptor subtypes. In addition, some BZDs are more potent than others or are eliminated from the plasma more slowly than others. These complex pharmacological activities explain the different clinical effects (e.g. anxiolytic, hypnotic, anticonvulsant, amnesic and muscle relaxant) of BZDs. Since their introduction, BZDs have been usually classified into two main groups (*medium/long half-life* and *short/ultrashort half-life*), according to their elimination plasma half-life ($t_{½}$) and their metabolic pathways (e.g. demethylation, hydroxylation, active metabolite) [8, 9]. Tables 11.1 and 11.2 summarize the main pharmacokinetic and metabolic characteristics of BZDs.

Z-drugs are a non-benzodiazepine class of psychotropic drugs, commonly used in clinical practice as hypnotics for the short-term treatment of insomnia. Z-Drugs, also defined as *hypnotic benzodiazepine receptor agonists* (HBRA), include the following agents: *zolpidem*, *zopiclone* and *zaleplon*. Z-Drugs bind to the BZD receptor subunit of the GABA-$_A$ receptor. The peak plasma concentration is attained 1–2 h after intake. These agents are primarily metabolized in the liver and have a short elimination half-life ranging from 2 to 6 h [10]. Z-Drugs are generally well tolerated and initially thought to be less addictive and/or habit-forming than BZDs, but several cases of dependence, abuse and misuse have also been reported in patients treated with such drugs [11].

Table 11.1 Medium-long plasma half-life BZD

BZD with medium-long plasma half-life
Drug name *Pronordiazepam-like compound*: prazepam, clordesmetildiazepam, clobazam, desmethyldiazepam, flurazepam, chlordiazepoxide, diazepam, ketazolam, medazepam, pinazepam, quazepam *Nitro-BZD*: nitrazepam, flunitrazepam
Pharmacokinetic features *Plasma half-life*: more than 24 (24–100 h) including active metabolites with long half-life *Metabolism*: demethylation to *nordiazepam*, hydroxylation and conjugation by glucuronic acid
Interactions: SSRIs, oral contraceptives, can decrease hepatic hydroxylation and increase plasma levels of these BZDs; alcohol and CNS depressant drugs induce sedative and hypotensive effects

Table 11.2 Short and ultrashort plasma half-life BZD

(A) **Short/ultrashort plasma half-life BZD**s
Drug name Alprazolam, bromazepam, brotizolam, estazolam, triazolam
Pharmacokinetic features *Plasma half-life*: 2–6 h for triazolam, brotizolam, lormetazepam; 6–24 h for other BZDs *Metabolism*: hydroxylation and conjugation with glucuronic acid; no active metabolites
Interactions: SSRIs and oral contraceptives can inhibit hepatic hydroxylation and can increase Plasma levels of these BZDs Sedative effects and hypotension when combined with alcohol
(B) **Short/ultrashort plasma half-life BZD**s
Drug name *Oxazepam-like BZD* (i.e. camazepam, lorazepam, lormetazepam, oxazepam, temazepam)
Pharmacokinetic features *Plasma half-life*: less than 24 h *Metabolism*: conjugation with glucuronic acid; no active metabolites
Interactions: No relevant pharmacokinetic drug interactions. Severe sedative effect and risk of hypotension when combined with alcohol or CNS sedative drugs

11.3 Use of BZDs and Z-Drugs in Pregnancy

Pregnancy represents a period of important physical and psychological changes, to the extent that some women may have difficulties in handling their mixed feelings of happiness and fear or concern for their future life. In Western countries, several epidemiological studies documented a plethora of psychiatric disorders and/or symptoms that may arise or worsen, during pregnancy, which may require a timely psychopharmacological treatment and/or a psychological support. Consequently, it is also very important not to underestimate the occurrence of initial symptoms like tension, sadness, emotional distress, irritability and sleep difficulties affecting a pregnant woman, as these symptoms may be *warning signs* of a more severe psychopathological condition.

Anxiety and sleep difficulties represent one of the most frequently occurring psychopathological conditions during pregnancy, with a prevalence rate estimated from 8% to 12%, according to different epidemiological studies [12]. Anxiety symptoms and insomnia can be moderate but persistent and, in many pregnant women, can lead to relevant levels of distress and impairment of quality of life. In many cases anxiety states occur in comorbidity with clinically relevant depressive symptoms.

It has been documented that BZDs and Z-drugs are medications prescribed also in women during pregnancy. An epidemiological survey involving about 15,000 pregnant women in 22 countries showed that BZDs were prescribed to 3.0% of them, whilst psychotropic drugs were prescribed to 3.5% of the overall sample. A striking variability between different countries in prescription rates during pregnancy has been also reported: BZDs were prescribed in 3% of 10,144 French mother-infant pairs, whilst, in a US sample of about 130,000 pregnant women drawn from eight health maintenance organizations, BZDs were prescribed from 0.001% to 0.14% of the sample; a prescription rate of 0.1% was reported in Germany [13–15].

There is still an uncertainty regarding the pharmacological treatment of sleeping disorders during pregnancy, even though it has been reported that 64–88% of pregnant women experience disturbed sleep during pregnancy, compared to 20–38% amongst women in the general population, in Western countries [16]. Moreover, it has been estimated worldwide that about 85% of psychotropic medications prescribed for affective disorders during pregnancy are BZDs and Z-drugs [17].

Further and more detailed epidemiological investigations are needed to better understand not only the rate and trend of anxiolytic and hypnotic drug prescriptions during pregnancy but also their pattern of use, i.e. the dosage, length of treatment, drugs used in association and clinical reasons for drug prescription.

11.4 Risk of Congenital Major Malformations

11.4.1 Benzodiazepines

Overall, the use of BZDs, during early pregnancy, has been considered problematic, for a long time, due to the risk of inducing birth defects, particularly cleft lip or palate (oral cleft). However, recent investigations, systematic reviews and meta-analytic studies indicate that the prescription of BZDs, in early pregnancy, should not be considered a contraindication anymore, even though, in clinical practice, their utilization needs a careful risk/benefit assessment in each pregnant woman. In fact, whilst the first epidemiological studies investigating the neonatal safety of BZD exposure in early pregnancy reported an increased relative risk for specific birth defects, others more recently failed to confirm such risk [1, 2].

In addition, despite some studies describing an association between a BZD exposure and the risk of some birth defects, the absolute risk of this malformation remains very low [18, 19]. Two papers, published more than 10 years ago,

reported data concerning the risk of congenital major malformations (MMs) amongst women exposed to BZDs during the first trimester of pregnancy [18, 19].

In the meta-analysis by Dolovich et al. [18], including 11 cohorts and 12 case-control studies, whilst data from cohort studies did not show any association between BZD exposure during pregnancy and the risk of MMs (including oral cleft), case-control studies reported a fairly low relative risk for such malformation. However, a recent update to this meta-analysis by Enato et al. [20], including a total of nine studies with over one million pregnancies and 4500 newborns exposed, concluded that "while BZDs do not appear to increase the teratogenic risk in general; case-control studies suggest a twofold increase in the relative risk of oral cleft"; moreover, case-control studies addressing the specific risk of cardiac malformations did not detect any statistical significant association. A systematic review by Iqbal et al. [19] did not consider BZDs as a class, but focused on the risk concerning single agents; the main conclusion of this study was that prescribing BZDs in the first trimester of pregnancy should be considered "substantially reassuring". However, an increased relative risk of MMs concerning some BZD agents was found in few reports, even though the absolute risk was very low and no specific pattern of malformations was identified. For example, in the study by Bonnot et al. [21], congenital anal atresia was reported in a rate (i.e. absolute risk) of approximately three cases every 10,000 unexposed newborns; considering that lorazepam determines a sixfold increase of the risk after in utero exposure, it raises to less than 20 cases every 10.000 newborns, i.e. less than 0.2% of newborns.

Amongst the few studies conducted to investigate the risk of heart structural anomalies in newborns exposed to BZDs in the first trimester of pregnancy, no increase of relative risk was reported, compared to the rate of general population (infants not exposed) [16].

An original study conducted by Oberlander et al. [22] highlighted the combined effect of taking SSRIs and BZDs in combination, suggesting that such dual drug exposure, rather than the BZDs alone, was associated with an increased, even though small, relative risk of congenital heart defects (RR, 1.2, CI, 0.18–2.18).

However, these findings have not been confirmed in more recent investigation focusing on the same topic by Reis and Kallen [23], using data from a Swedish National Health Register. Participants included (a) 10,511 infants whose mothers were prescribed an SSRI but no other CNS-active drugs, (b) 1000 infants of women who were prescribed BZDs and no other CNS-active drugs, and (c) 406 infants whose mothers were treated with a combination of an SSRI and a BZD. None of the three groups showed a higher relative risk of MMs or any cardiac defect when comparison was made with the risk in general population. The adjusted risk ratio for the combination of SSRIs and BZDs was 1.17 (95% CI, 0.70–1.73). A major limitation of the present study was that, despite the large number of women included, relatively few had a concomitant use of an SSRI and a BZD.

A UK large population-based cohort study compared the rate of MMs: (a) in newborns exposed to BZDs in the first trimester of pregnancy, (b) in newborns of untreated mothers affected by depression and/or anxiety and (c) in infants of healthy

mothers (control group). The prevalence rate found in this investigation was 2.7% in 1.159 infants of mothers who received a prescription of diazepam, 2.9% in 379 infants with temazepam, 2.5% in 406 infants with zopiclone and 2.7% in 19.193 children whose mothers were diagnosed as affected by depression and/or anxiety but with no drug exposure. When compared with a rate of 2.7% in 351.785 children of mothers without any diagnosed depression/anxiety nor medication use, the adjusted odds ratios were 1.02 (99% confidence interval 0.63–1.64) for diazepam, 1.07 (0.49–2.37) for temazepam and 1.27 (0.43–3.75) for other anxiolytic/hypnotic drugs and 1.01 (0.90–1.14) for unmedicated depression/anxiety. Risks of system-specific malformations were generally similar in children exposed and not exposed to such drugs [16].

Therefore, it may be concluded, according to recent original studies, as well as overviews and guidelines, that the use of BZDs during pregnancy should be substantially considered safe at least in terms of risk of congenital birth defects [14, 24, 25].

11.4.2 Z-Drugs

Less information concerning the foetal and neonatal safety of Z-drugs have been so far published. Few studies focused on *zolpidem* use in early pregnancy. A prospective study carried out on 45 pregnant women who used zolpidem in comparison with a group of untreated pregnant women did not report any MMs in newborns exposed in utero [26]. A retrospective cohort study did not report significant differences in rates of MMs between a group of pregnant women who were treated with zolpidem and an untreated control group [27].

Only a population-based retrospective cohort study has been published to evaluate the safety of *zaleplon* in early pregnancy, by reporting no increased risk of MMs [28].

The safety of *zopiclone* in newborns exposed in utero has been explored so far in two studies, which did not report any MMs [29, 30].

More recently, data collected from 1995 to 2007, coming from the *Swedish Medical Birth Registry*, selected 1318 women who reported the use of Z-drugs in early pregnancy. They gave birth to 1340 infants who were compared to infants born during the same study period from a control group (women not exposed to such drugs in early pregnancy) [31]. An excess of smoking, use of other drugs and above all psychoactive drugs were recorded in women exposed to Z-drugs, even though no increased risk for MMs was found in the newborns exposed [31].

Also, the above-mentioned population-based cohort study by Ban et al. [16] compared the risk of MMs in (a) children exposed to anxiolytic/hypnotic drugs (including zopiclone), in the first trimester of pregnancy, (b) children of untreated mothers affected by depression and/or anxiety during pregnancy and (c) infants of mothers without any psychiatric condition. A rate of MMs of 2.5% was reported in 406 newborns exposed to zopiclone, compared to a rate of 2.7% reported in 19,193 children whose mothers had an untreated depression and/or anxiety disorders

during pregnancy [16]. The authors concluded that "we have not found evidence for an increase of MMs in children exposed to BDZ and non-benzodiazepine hypnotics in the first trimester of pregnancy" [16].

11.5 Perinatal Complications

11.5.1 Benzodiazepines

During the second and third trimester of pregnancy, BZD exposure could be associated with an increased risk of some perinatal complications (PCs), particularly preterm birth, low birth weight and neonatal withdrawal syndrome (NWS). NWS is a condition affecting about 25% of newborns exposed to BZD late in pregnancy, including signs such as somnolence, irritability, difficulties with sucking, tremors, tachypnea, gastrointestinal upset, hypoglycaemia and hyperreflexia. The NWS appears generally within a week after birth and can last from a few days up to 3/4 weeks [32].

The use of BZDs, especially at high dosage, just before delivery has been associated to an *infant floppy syndrome* (IFS), a well-known syndrome characterized by floppiness or general muscular hypotonia at birth or in early life, affecting the limbs, trunk and the cranial-facial musculature. It should be observed, however, that IFS can be also induced by a variety of neuromuscular and central nervous system disorders (including genetic and/or metabolic deficits); therefore its association with BZD exposure before delivery needs to be better investigated [33]. It has been suggested that gradually tapering the daily dose of BZDs some weeks before delivery may be useful to minimize the neonatal withdrawal symptoms; however, this clinical strategy has not been proved effective in all cases. In addition, a BZD discontinuation could induce a withdrawal reaction in pregnant woman, especially amongst those who have been taking higher doses of BZDs for several weeks during the gestation [19].

Furthermore, a common clinical practice reported that most newborns presenting some withdrawal symptoms improve and recover soon, after a few days or sometimes weeks, without any long-lasting sequelae. No long-term clinical relevant consequences have been so far reported in infants exposed in utero to BZDs [2, 19].

11.5.2 Z-Drugs

No differences in pregnancy outcomes, delivery method, preterm delivery, birth weight and other neonatal safety indexes have been reported in a Canadian prospective cohort study evaluating the risk of infants exposed to zopiclone in late pregnancy [29].

A retrospective cohort study compared a sample of 45 pregnant women in treatment with zolpidem for insomnia with untreated pregnant women (control group) [26]. Pregnant women who took zolpidem were more likely to have gestational hypertension and anaemia, as well as a greater chance of a caesarean delivery compared to the untreated group. The rates of preterm delivery and low birth weight were, respectively, 26.7% and 15.6% in the zolpidem-exposed group and 13.3% and

4.4% in the matched comparator. However, although there were no statistically significant differences in the outcome analysed, the zolpidem-exposed cohort had higher rates of low birth weight and preterm delivery than the matched controls. The authors underlined that it is still unclear if these outcomes were driven by zolpidem exposure and/or sleep disturbance in pregnancy warranting prescription intervention. In addition, women who reported longer-term zolpidem use during pregnancy (≥10 weeks) did not experience a higher rate of PCs.

Overall, even though relative reassuring findings have been here presented, further studies specifically focusing on short- and long-term infant outcomes are needed, in order to better investigate the foetal/neonatal safety of Z-drug exposure during early and late pregnancy.

11.6 Conclusions

Overall, according to the best recent cohort studies, overviews and guidelines, BZD and Z-drug exposure during early pregnancy seem not to be associated with an increased relative risk of congenital MMs.

However, it should be observed that, only in case-control studies (but not in cohort studies), a statistical significant association between BZD foetal exposure and some birth defects was found, even though the absolute risk of such identified defects was low.

To explain the discrepancy in the results of such studies, it is worthwhile to consider that most of the first original investigations suffer from a number of methodological flaws, such as the lack of a careful report of BZD patterns of use in pregnancy (i.e. time of exposure, dosages, reasons for drug prescription, etc.), possible influences of recall biases (linked to case-control design) and the lack of control for relevant confounding risk factors (i.e. the presence of a severe psychiatric and/or organic disorder, alcohol abuse, smoking and concomitant medications).

There is a general agreement that BZD exposure during the second and/or third trimester of pregnancy can be associated with an increased risk of neonatal and gestational complications, particularly preterm birth, low birth weight and neonatal withdrawal reactions (including the infant floppy syndrome). Most of such adverse events, however, are not severe and improve after a few days/weeks without any long-lasting sequelae.

No increase in the risk of infant neurobehavioral and cognitive anomalies has been so far reported in the few follow-up studies focused on this issue. Notwithstanding, most data on the safety of BZD exposure during early and late pregnancy seem to be quite reassuring. However, there is still a need to perform further prospective cohort studies, based on adequate large databases, enrolling and following women from the first prenatal visit to the end of pregnancy and in the postpartum period, with a regular clinical monitoring of their psychopathological conditions and drugs prescribed and with a standardized assessment of neonatal outcome in the long term.

Finally, it is strongly recommended to treat pregnant women with antianxiety and/or hypnotic drugs, only in the case of severe insomnia and/or acute anxiety

states, where other effective therapeutic options, particularly psychological treatment using the *cognitive-behavioural therapy* [CBT]) have failed. Amongst the BZDs, it should be preferred, as first-line option, agents with a short-medium elimination half-life and with no active metabolites (i.e. oxazepam-like compounds).

The dosage and length of the treatment should be accurately individualized in each pregnant woman, to prescribe the lowest effective dose for the time strictly necessary, according to the clinical condition. Such clinical practice is crucial to prevent or minimize neonatal adverse events, particularly the risk of severe withdrawal reactions and the infant floppy syndrome.

In Table 11.3, recommendations concerning the use of anxiolytic and hypnotic drugs in routine clinical practice have been shortly reported, according to the recent evidence-based information and expert opinions.

Table 11.3 Expert recommendations based on scientific evidence and clinical experience

The prescription of BZDs and Z-drugs during pregnancy should be reserved to severe cases of acute anxiety symptoms and insomnia, where effective non-pharmacological treatment (e.g. CBT) has failed or is not effective enough
BZDs are drugs not indicated in monotherapy to treat patients with general anxiety disorders, obsessive-compulsive disorder and major depression; in such disorders second-generation antidepressants (such as SSRI) are considered the first-line pharmacological option
BZDs should not be used for several months, but short-intermittent use is preferable to avoid potential condition of dependence or misuse; the discontinuation must always be carried out gradually, according to the dosage used and the length of treatment
When considering the risks and benefits of anxiolytic and hypnotic drugs, clinicians should also consider the risks of untreated insomnia and acute anxiety in pregnancy, which may lead to physiologic effects as well as a reduced level of self-care, worsening mood and impaired functioning
Nowadays, BZDs and Z-drugs are not considered at risk of teratogenesis, as recent studies did not support an increased risk of major malformations in newborns early exposed in utero, as compared with unexposed control group
Exposure to BZDs in late pregnancy may be responsible of some gestational (preterm birth) and neonatal complications (i.e. withdrawal syndrome, including the infant floppy syndrome), which in most newborns improve in few days or weeks, without any long-lasting sequelae. In any case, an infant clinical monitoring by a paediatrician during the first weeks after birth is strongly recommended
The woman (and his husband/partner/family) should be well informed about the potential risks of the drug treatment and those resulting from the nontreatment. As well, the clinicians should be sure that all information provided have been clearly understood; an informed signed consent must be also collected
The dosage and duration of a drug treatment must be always individualized in each woman, in order to establish the minimum effective therapeutic dosage and the appropriate length of drug treatment
Amongst BZDs, drugs with short or medium elimination half-life and no active metabolites should be preferred as first-line options, due to their better pharmacokinetic and metabolic profile
Women treated with BZD and Z-drugs during pregnancy should give birth in a general hospital where there is a *neonatal intensive care unit*. This is important to provide effective and timely treatment in case of severe neonatal adverse reactions

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Benzodiazepines and Z-Drugs During Lactation

12

Faruk Uguz

12.1 Introduction

Puerperium is an important period in women, during which the onset and exacerbation of psychiatric disorders may be observed. Anxiety disorders in this period are frequent and affect up to 39% of women [1]. Some mothers with anxiety disorders need to be treated with drugs due to a high severity of symptoms, comorbidity with depression, and severe functional impairment, including care for her baby. Although antidepressants are first-line drugs used in the clinical practice for the treatment of these patients, the use of benzodiazepines for a short period is not rare. On the other hand, many postpartum women experience sleep disturbances including poor sleep quality and insomnia [2]. In addition to antidepressants and benzodiazepines, non-benzodiazepine hypnotics (Z-drugs) are important pharmacological options in patients with insomnia [3].

Breastfeeding is one of the major challenges in the treatment of women with psychiatric disorders. It is well known that breast milk is the gold standard for infant nutrition and has indispensable lifetime benefits. Breastfeeding is associated with reduced morbidity, mortality, and occurrence of illnesses via factors including gastrointestinal mucosal maturation and decrease of the incidence of infection, alteration in the gut microflora, as well as immunomodulatory and anti-inflammatory factors, hormones, growth factors, and cytokines [4, 5]. Therefore, pharmacological agents that are recommended for postpartum women should be safe and not interfere with breastfeeding as much as possible. Considering that psychotropic medications may be excreted into the breast milk to at variable degrees, safety data on psychotropic drugs during lactation is essential to minimize infant exposure and subsequent adverse effects [6].

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12.2 Benzodiazepines

Benzodiazepines, especially diazepam and lorazepam, are frequently used not only for the treatment of maternal anxiety disorders but also for the management of acute neonatal seizures and status epilepticus in children or as prophylactic drugs for the management of febrile seizure in children [7–9]. Despite a long history of clinical usage, data so far published on the safety of benzodiazepines in breastfeeding women are limited. However, the available scientific evidence does not demonstrate any contraindication for breastfeeding during maternal use of these medications [4]. In general, shorter-acting agents such as alprazolam and lorazepam are preferred to longer-acting agents such as diazepam and clonazepam that show a high risk of accumulation in infants through breast milk. In addition, among breastfeeding women with psychiatric diagnoses, it is recommended a brief and intermittent usage of benzodiazepines at low doses. Moreover, repeated doses should be avoided, if possible [4, 10, 11]. Table 12.1 summarizes the recommendations by this paper regarding the use of benzodiazepines during breastfeeding.

It has been reported that the most commonly used benzodiazepines in the lactation period are lorazepam (52%), clonazepam (18%), and midazolam (15%) [12]. Recently, data from 124 breastfeeding mothers in the Motherisk Program at The Hospital for Sick Children in Toronto, Ontario, have suggested that only 1.6% of infants exposed to benzodiazepines had central nervous system (CNS) depression defined as sleepiness, poor latching, not waking up for breastfeeding, limpness, or lack of response to stimuli. The authors also noted that the infant sedation rate in their study was similar to that previously reported with exposure to acetaminophen [12]. It has been reported that adverse events such as sedation, lethargy, feeding difficulties or weight loss, drowsiness, apnea, restlessness, and irritability were observed in a considerable proportion (17–50%) of infants exposed to benzodiazepines, particularly if the mothers used the drugs for a long period [11, 13, 14]. These adverse effects are mostly resolved within 2 weeks following discontinuation of the medication [14]. In addition, some withdrawal symptoms (e.g., tremor of the

Table 12.1 Expert recommendations based on scientific evidence and clinical experience

Due to its tremendous beneficial effects, continuation of breastfeeding should be the main goal in clinical practice
The available limited data suggest that there is no clear contraindication regarding the use of benzodiazepines and Z-drugs during the lactation period
Benzodiazepines and Z-drugs should be used for a short term, with intermittent and as low doses as possible
Shorter-acting benzodiazepines are preferred to longer-acting ones
Infants exposed to benzodiazepines via breast milk should be carefully monitored with respect to CNS depression and feeding problems
Among benzodiazepines, lorazepam owns the largest data on safety in breastfed infants
Clonazepam should not be used during breastfeeding if it is not necessary
The best safety profile of benzodiazepines frequently used in breastfeeding women is presented as midazolam > lorazepam > oxazepam/alprazolam > diazepam > clonazepam

extremities, diarrhea and vomiting, restlessness, inconsolable crying, irritability, growth retardation due to feeding problems, sleep disturbances, and tendency for convulsions) may be observed in infants of women who discontinue after a long-term usage of benzodiazepines [11, 13]. These symptoms can appear within a few days to 3 weeks after the discontinuation, and their resolution may take weeks [13]. Therefore, benzodiazepines used for a long-term period by breastfeeding women should not be discontinued suddenly.

12.2.1 Diazepam

Safety data of approximately 20 cases using diazepam have been published in the literature [4, 12, 14]. The available data suggest that diazepam is excreted in small amounts into breast milk [11]. It is usually undetectable in the plasma of most infants. Milk to plasma ratio (M/P ratio) and relative infant dose (RID) for diazepam have been reported to be 0.2–0.58 and 3–7%, respectively [4, 10, 11, 15]. Adverse events have been rarely reported [4]. Accumulation risk in infants due to the long half-life of diazepam is an important restrictive factor for its usage during the lactation period. Additionally, long-term use by nursing mothers can result in sedation and lethargy that may lead to severe feeding problems and weight loss in the infants. Therefore, the use of diazepam chronically and/or at high doses should be avoided, and breastfed infants should be carefully monitored for feeding, weight, and sedation [11, 13].

12.2.2 Clonazepam

Available data indicate that the use of clonazepam during the lactation period was about twofold higher than diazepam [4]. Limited available data suggest that it has similar safety features as diazepam such as a low M/P ratio (0.33), RID value (2.5%), usually undetectable plasma levels, and a high accumulation risk in infants [4, 11, 14, 16]. On the other hand, a descriptive study based on the French Pharmacovigilance Database reported that 3.7% (n = 5) of drug-induced adverse reactions via breastfeeding was related to the use of clonazepam [17]. Infants exposed to this benzodiazepine should be carefully monitored for CNS depression, because adverse effects in infants, especially apnea and sedation, have been reported with this medication [4, 13]. Long-term use of clonazepam is not recommended; usage should be either a single dose and/or few doses as possible with caution [18].

12.2.3 Alprazolam

There are 24 cases that reported the use of alprazolam in breastfeeding women in the literature [4, 12, 14, 19]. Oo et al. [19] reported that the mean M/P ratio and RID value for alprazolam were 0.36 and 3%, respectively. The authors also noted that

infant plasma levels of this agent were below the detection limits. Although there are some adverse events reported in infants including CNS depression [12], irritability, sleep disturbances, sedation, and drowsiness [4, 14] in the literature, their incidence is low. Being an intermediate-acting benzodiazepine, alprazolam is more advantageous for use during breastfeeding compared to diazepam and clonazepam. However, if used long term, the breastfed infant should be monitored as closely as possible for CNS effects on the infants. It is recommended that usage should be either a single dose or as few doses as possible; however, long-term use and/or high doses are possible with caution [18].

12.2.4 Lorazepam

Lorazepam is an intermediate-acting benzodiazepine that has the largest reported data ($n = 87$) in the literature [4, 12]. While M/P ratio is 0.15–0.26, data on RID is not available [11]. It has been shown that lorazepam is excreted into breast milk in low concentrations [13]. Kelly et al. [12] reported no CNS depression in infants of 64 breastfeeding women taking lorazepam. When it is considered that lorazepam does not have any accumulation problem in the infants and that the exposure via breast milk is not associated with adverse effects on the infants [13], lorazepam appears to be most preferable benzodiazepine in the lactation period. Using this drug in a single dose and/or in a low dose is acceptable; however, long-term use and/or high doses are possible with caution [18].

12.2.5 Oxazepam

Half-life of oxazepam in maternal plasma is shorter than alprazolam and lorazepam. Its passage into breast milk is relatively low as shown by its reported M/P ratio (0.1–0.3) and RID value (0.7%). Moreover, to date, no adverse effects have been observed in the infants. However, the availability of safety data from very few cases in the literature ($n = 4$) is a major issue deterring the prescription of oxazepam during the lactation period [4]. For this reason, usage should be either a single dose or as few doses as possible; however, long-term use and/or high doses are possible with caution.

12.2.6 Midazolam

Although midazolam is one of benzodiazepines that is frequently used during lactation, its usage in patients with psychiatric diagnosis is very rare [18]. Incidence of adverse events in the infants is low. Other advantages of this drug are a short half-life, being undetectable in plasma of most infants, and low M/P (0.2) ratio and RID value (<1%) [4, 20]. Although midazolam may be used as a single dose with caution in patients with severe agitation, it does not appear to be appropriate for long-term usage since it is an intravenous anesthetic agent [20].

12.3 Z-Drugs

The Z-drugs including zaleplon, zopiclone, eszopiclone, and zolpidem are defined as nonbenzodiazepine hypnotics and are currently more frequently prescribed compared to benzodiazepines for the treatment of insomnia [21]. Since few studies have suggested their relative safety in breastfed infants, these agents may be alternative medications to benzodiazepines for the treatment of primary insomnia during lactation [11].

There is one study with small sample size regarding the use of zaleplon ($n = 5$), zolpidem ($n = 5$), and zopiclone ($n = 12$) in the literature. Darwish et al. [22] reported that M/P ratio for zaleplon was 0.50 and the infant dose was below 1% of the maternal dose. These data indicate that transfer of zaleplon via breast milk to the infant was in a very small quantity that was unlikely to be clinically important. Similarly, the excretion of zolpidem in human milk was reported to be very low (M/P ratio = 0.13) [23]. The average M/P ratio and weight-adjusted infant dose for zopiclone were found to be 0.51 and 1.4%, respectively [24]. However, clinical effects of these medications on breastfed infants remain unclear. Therefore, these medications should be used with caution in breastfeeding women with insomnia.

12.4 Conclusion

The corpus of data in the literature on the safety of psychotropic medications in breastfed infants does not correlate with the frequency of their usage. Although the available reports do not suggest a clear contraindication for the use of benzodiazepines, their long-term effects on the breastfed infants remain unclear. Therefore, decisions concerning these medications during the lactation period should be made on the basis of the need to treat the mother and their potential side effects in the infants. Single administration or a short-time usage at low doses seems to be compatible with breastfeeding. The exposed infants should be carefully monitored by the mother and pediatricians during maternal use of benzodiazepines. Short-acting drugs, especially lorazepam, are more preferable compared to long-acting ones. Limited available data suggest that Z-drugs may be alternative drugs to benzodiazepines in breastfeeding women with primary insomnia.

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Part III

Pharmacological Management of Psychiatric Disorders During the Perinatal Period

Major Depression

13

Sonya Rasminsky, Erin Murphy Barzilay, and Vivien K. Burt

13.1 Introduction

Since half of all pregnancies are unplanned and close to 10% of women aged 20–39 in the United States now take antidepressants [1], all psychiatrists who treat women of childbearing age should be familiar with perinatal psychiatry. Depression during pregnancy is common, and the use of antidepressants in pregnancy has been steadily increasing over the past two decades [2–4]. The postpartum period is an especially vulnerable time for mood disorders, particularly for women with histories of perinatal depression.

After a careful analysis and consideration of both the strengths and limitations of the evidence-based data on psychopharmacologic management of depression in pregnancy and the postpartum, the challenge for psychiatrists who treat women of childbearing age is to facilitate the generation of a plan that optimizes outcomes for their patients while considering possible implications for their potential offspring. Given the underlying reality of an uncertain future, treatment recommendations should be carefully individualized, taking into consideration both the most current scientific data and the patient's values and preferences.

Sensitive to the lingering stigma associated with psychiatric disorders, women who struggle with perinatal depression are often reluctant to voice their suffering to even close family or friends. The internet is replete with advice, often based on personal experiences from women who themselves are depressed; new publications about antidepressants in pregnancy garner dramatic headlines regardless of their scientific merit. Faced with worrisome information in the media, pregnant depressed women often hesitate to seek help that may include necessary advice about medication. Since depression is often accompanied by uncertainty, poor self-esteem,

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and a lack of confidence, these women fear that they will be viewed as weak, flawed, or complaining. For women who struggle with perinatal depression, their sense of incompetence often contributes to a feeling of isolation and alienation.

Fortunately, women with histories of depression are increasingly requesting psychiatric consultation because they wish to plan ahead in order to maximize positive outcomes for themselves and their babies. Women present at various points: some are not currently pregnant but may become pregnant in the future; some seek treatment during different trimesters of pregnancy; and some are newly postpartum or present later in the first postpartum year. Unfortunately, many women and referring clinicians have limited knowledge about treatment options in these settings, and the knowledge they do have is often tainted by misinformation and misunderstanding.

Like all patients who present for psychiatric treatment, women's needs vary based on psychiatric and medical history, psychosocial stressors, personal and partner values, and a myriad of other factors, all specific to each patient. Nevertheless, a unifying goal when treating women in the perinatal period is to maximize mental health and recognize that maternal depression impacts the entire family.

13.2 Decision-Making in the Perinatal Period

Pharmacologic treatment of depression during pregnancy has become increasingly common, with approximately 8% of women taking antidepressants during pregnancy [3]. Traditionally, the decision about whether to take psychotropic medications during pregnancy has been described as a risk-benefit analysis, when it is more correctly framed as a risk-risk analysis. Since there are no randomized placebo-controlled studies on the effects of psychotropic medication and depression (or other psychiatric disorders) on pregnancy and infant outcomes, conclusions are largely based on case-control or cohort studies. Many of these are observational studies derived from clinical databases and thus are subject to confounding variables. The most troubling of these is that existing studies have not been able to analyze whether adverse outcomes are associated with antenatal psychotropic medications or the condition for which the medications have been prescribed ("confounding by indication"). It is incumbent upon clinicians to help patients sort through alternative options while understanding the incomplete and uncertain nature of available data.

For some women, the decision may be to "watch and wait" with close psychiatric monitoring without immediate pharmacologic intervention, often with ongoing psychotherapy. For others, the choice may be an antidepressant, possibly with other psychiatric medications when needed, to relieve depression and associated symptoms. Data on various treatment approaches should be deciphered for each patient, with an understanding that no one study is perfect. Patients need to be reminded that the background risk of congenital abnormalities is 2–4%. Using an honest, empathic approach, discussion should ideally incorporate a mutual understanding that to expect absolute perfection is to guarantee disappointment. The goal is to help each

patient understand the available data (with its strengths and limitations) and then to arrive at a decision that she can most comfortably live with.

No two patients are the same. What one woman can accept in terms of risk is different from what another woman deems reasonable. How a woman has addressed stressful decisions in the past is likely to inform how she will deal with decisions regarding psychiatric treatment during pregnancy and the postpartum. Risk assessment should optimally include both the perinatal patient and her partner. A stable and supportive family and social network are critical to helping the pregnant or postpartum woman live comfortably with the treatment regimen she has chosen. It is often advisable for the treating clinician to facilitate other avenues of support (e.g., individual psychotherapy, couples' counseling, perinatal support groups). Frequently, although decisions have been made to move forward with pharmacologic treatment, doubts and new questions arise as new studies are published and reported in the popular media. Clinicians should be readily available to review existing and new data and its interpretation in ways that are clear and understandable for the patient.

13.3 Assessment of the Perinatal Patient

The treatment of perinatal depression begins with a thorough clinical and psychosocial assessment, with the goals both of assessing personal risk and also eliciting patient knowledge and preference. Because a large body of information already exists on the assessment of the general psychiatric patient, this section will focus on the unique aspects of the assessment of women who either desire to become pregnant or are currently pregnant or postpartum. For a detailed list of the components specific to assessing the perinatal patient, see Table 13.1.

The initial evaluation should include questions about the patient's feelings and expectations regarding pregnancy and motherhood. Her experience with previous pregnancies (both emotionally and obstetrically) will inform those expectations. In a woman who is not yet pregnant, an exploration of her relationship to her body, previous weight changes, and eating habits may be informative regarding how she will experience bodily changes and weight gain during pregnancy. If the patient is already pregnant, was the pregnancy planned? What are the patient's thoughts regarding plans for delivery and infant feeding (breastfeeding, pumping, or formula), and what are her resources for support during and after pregnancy?

The perinatal postpartum patient should be specifically observed for interactions with her baby (and if possible, other children in the family). These interactions often reveal the quality of attachment and bonding between mothers and their children, which may be compromised in the setting of maternal mental illness. How a mother reacts to her children's needs should be assessed. Is she able to soothe her baby and respond appropriately to hunger or sleep cues, or does she become frustrated and distressed? Observations of both maternal and infant

Table 13.1 Assessment of the perinatal patient: clinically significant considerations

Component	Consideration
Clinical issues	Assess for psychiatric symptoms in relation to: • Pregnancy (past or present)—including history of birth trauma or pregnancy loss • Postpartum (past or present)—include whether breastfeeding, supplementing with formula, or weaning • Premenstrual mood changes • History of abortion • Infertility treatment Inquire about past or present symptoms or signs of eating disorder or body image perceptions that may be particularly problematic during pregnancy or the postpartum
Medications	• Inquire about effectiveness: What has been helpful in the past? Is the patient taking medications now? Are they effective? Any side effects? • Inquire about beliefs and understanding regarding the use of medication during pregnancy, breastfeeding
Alcohol and drug use	• Inquire about the past or present use of alcohol or illicit drugs • Inquire about the use of pain killers • Rule out possible covert use
Family psychiatric history	Include history of psychiatric instability in female family members in relation to pregnancy, postpartum
Medical history	Rule out illnesses that may emerge or worsen in pregnancy or postpartum (e.g., lupus, thyroiditis, fibromyalgia)
Social and developmental history	• Inquire about current relationships – is there a partner; is he/she supportive, psychologically aware? • Note history of emotional response and level of functioning in response to past transitions, role changes, or traumatic events • Assess level of economic support as this may relate to ability to get extra help if needed for childcare and other responsibilities • Inquire about religious or cultural views that may be relevant to the nature of interaction with the baby or may influence ability to understand and accept treatment recommendations (e.g., possible recommendation to achieve psychiatric stability prior to attempting conception)
Views and plans regarding pregnancy, postpartum, and parenthood	• Inquire about expectations regarding pregnancy, motherhood • Inquire about plans for antenatal care, delivery, postpartum preparations, childcare, breastfeeding
Evaluate level of functioning	• If postpartum, observe for interactions, bonding with baby, other children (especially other children at home)
Assess for issues of safety	• Inquire about thoughts of self-harm, harm to others (especially infant, if postpartum) • Establish whether any thoughts of harm are ego-syntonic or ego-dystonic • Connect with child welfare authorities if needed for further assessment

hygiene provide insight into a new mother's ability to care for herself and her baby.

In addition to assessing the potential for self-harm, any thoughts of harm toward infants and children are an essential component of the perinatal evaluation. In the event that a mother has thoughts of harming her child, it is important to assess whether these thoughts are ego-syntonic or dystonic. Ego-syntonic thoughts of harming one's child suggest psychosis and generally warrant intensive inpatient care. Ego-dystonic thoughts may be indicative of obsessive-compulsive illness that, while disabling, does not directly endanger the child. Only by carefully teasing out the nature of such thoughts can the astute clinician assess whether childcare authorities should be called for further evaluation of possible safety concerns in the home.

Newly pregnant women are at substantial risk for recurrence if they discontinue the medications that have kept them well [5]. Thus, recommendations regarding medication are based not only on the patient's current presentation but also on her history. Of particular importance to the perinatal assessment is a detailed history of response to prior treatment regimens during past pregnancies and postpartum periods, as this may guide future interventions.

A thorough reproductive history includes eliciting timing of menarche, menstrual irregularities, history of premenstrual psychiatric symptoms and response to hormonal birth control, infertility treatments, and number and outcome of past pregnancies. Since past response to hormonal changes may be predictive of psychiatric status during the perinatal period, this information can be a useful guide. A patient who is older or has a history of prior losses, miscarriages, traumatic deliveries, or repeated assisted reproductive procedures may understand and interpret available data quite differently from a younger pregnant woman with no past obstetrical stressors and considerable time ahead in which to achieve emotional stability prior to conception. Of particular importance is establishing a history of substance or alcohol abuse, especially perinatally.

Understanding the setting into which a baby is born is also essential. Social history includes a detailed understanding of the relationships within the family of origin, family of a partner (if involved), history of trauma, developmental difficulties, educational history, employment (including plans about returning to work after baby), financial means, relationship with partner, and social supports. A patient's personal history of parental figures may provide insight into her ability to function as she transitions into motherhood. A family history of mood disorders, particularly during the postpartum, increases the risk for perinatal depression. A patient's cultural and religious views of contraception, elective abortion, pregnancy, delivery, and breastfeeding should be discussed. What constitutes pathology for one patient may be a normal practice for another, and understanding the patient's core values and beliefs is integral to the collaborative decision-making process.

13.4 Risks of Untreated Maternal Disorders

Depressive symptoms affect approximately 10% of pregnant women, with 5.1% meeting criteria for probable major depression and 4.8% for likely minor depression [6]. Although pregnancy does not increase the risk for depression, for women who enter pregnancy euthymic and on antidepressant medication, discontinuation of their medication increases the risk for recurrence of their symptoms [5]. Depression during pregnancy carries with it significant morbidity for both the expectant mother and her developing fetus and can have a downstream impact on child development and risk of postpartum depression. Depression during pregnancy can include difficulty with following prenatal directions, eating a balanced diet, or gaining the recommended amount of weight, which in turn can have a negative effect on maternal obstetrical health and the health of the infant. Adverse effects of untreated depression during pregnancy may include hypertension, preeclampsia, preterm birth, spontaneous abortion, intrauterine growth retardation, and decreased breastfeeding initiation [7–10].

Women who are depressed are more likely to use alcohol, tobacco, and illicit drugs to manage their symptoms, leading to deleterious effects on the developing fetus. Seriously depressed pregnant women are at risk for suicidal thinking and attempts. When depression is severe, some women contemplate abortion, even when the pregnancy was desired and planned.

Women who experience depression during pregnancy have abnormalities of cortisol secretion, which affects the maternal hypothalamic pituitary axis and intrauterine hormonal milieu [11, 12]. It is hypothesized that this dysregulation may explain some of the negative outcomes for infants of depressed women. In addition, children born to mothers who are depressed in the perinatal period are at increased risk for mood and anxiety themselves [13].

Depression during pregnancy is a major risk factor for postpartum depression, which in turn affects child development. Maternal sensitivity to infant needs is essential for the healthy development of an infant's social, cognitive, and behavioral skills. Depressed mothers often show inconsistent parenting behaviors, contributing to adverse outcomes in their children. Recent research has shown that children exposed to early maternal depression may have increased behavioral problems and mental health symptomatology in early childhood [14].

For mothers who experience depression during the postpartum, it may be difficult to meet their infant's needs for the development of a secure attachment style, rendering the child at a higher risk for poor functioning in a range of developmental domains [15, 16]. Mothers with even subclinical or mild depressive symptoms report significantly impaired bonding with their babies. They report feeling resentful, angry, and distant from their babies and have difficulty feeling happy when their infants smile or feeling confident that they can care for their babies. Poor maternal-fetal attachment during pregnancy may contribute to abnormal maternal-infant attachment postpartum [17]. Successful treatment of maternal depression has been shown to have a positive impact for both mothers and their children [18].

Partners of mothers with postpartum depression are also at risk for the development of mood and anxiety symptoms [19]. When both parents are stressed, this places further strain on the family structure and makes it more difficult to meet the infant's needs.

13.5 Treatment of Depression During Pregnancy

Patient preference is always an important consideration in the treatment of perinatal depression: what one woman may regard as unacceptable (e.g., any report of possible increased risk of autism, no matter how small or how limited the data) may be a reasonable risk to another. While there is no one-size-fits-all strategy for managing depression during pregnancy, some general principles do apply. Table 13.2 outlines discussion points throughout pregnancy, and Table 13.3 outlines general guidelines for treatment.

If a woman is experiencing severe depression and is functionally impaired, or has a history of psychosis, suicide attempts, chronic depression, or relapses following medication discontinuation, treatment with antidepressants is advisable. In these cases, the risk of untreated maternal depression generally outweighs the risks associated with antidepressant exposure in utero. Some women with even moderate depression choose to remain on medication that keeps them well. In such cases, so long as known risks of both depression and antidepressant medications on both the mother and baby are reviewed, it is reasonable to continue pharmacologic management during pregnancy.

Nonpharmacological modalities vary from first-line options for treatment of mild disease to intensive treatment for refractory and severe depression. Psychotherapy can provide much-needed support, as well as practical tools for managing symptoms and understanding the contextual changes that accompany new motherhood. Manualized therapies such as interpersonal therapy (IPT) and cognitive behavioral therapy (CBT) have shown efficacy for treating antenatal and postpartum depression [20–22]. Bright light therapy is a noninvasive treatment for antenatal depression [23]. Two small studies have found transcranial magnetic stimulation (rTMS) to be effective and safe during pregnancy [24, 25]. On the other hand of the spectrum, electroconvulsive therapy (ECT) may be used during pregnancy for treatment of severe depression that has not responded adequately to pharmacological management. While some obstetrical complications have been reported with ECT use in pregnancy, it is largely a safe and effective treatment for patients with a heavy disease burden, often involving suicidality [26, 27].

13.5.1 General Principles of Treatment

The decision about which medication to use is determined by a number of factors, including a particular medication's safety profile, stage of gestation, symptom profile, personal history of response to particular medications, and family history.

Table 13.2 Discussion points for the treatment of depression in pregnancy

Pre-pregnancy
• Discuss options regarding medication, ideally involving partner (partner should participate in at least one visit)
– Review risks of depression during pregnancy, as well as risks of medication during pregnancy and lactation
– Include information about baseline risks of major malformations (2–4%) and miscarriage (20%)
• Explain that it may be necessary to adjust medication regimen to the lowest effective dose of the fewest medications
• Coordinate with Ob/Gyn about plan for medication during pregnancy
• Recommend starting prenatal vitamins
First trimester
• Review choices about medication during pregnancy
– If not done previously, review risks of depression in pregnancy, as well as risks of medication during pregnancy and lactation
– Discussion should focus on first trimester exposure, e.g., risk of major malformations and risk of miscarriage
• Monitor depressive symptoms and adjust medication dose as needed
• Elicit feelings about motherhood
• Discuss social supports during pregnancy
• Coordinate with Ob/Gyn
• Coordinate with therapist
Second trimester
• Review choices about medication during pregnancy
– Provide updates about any new data since last discussion
• Monitor depressive symptoms; dose may need to be increased given changing metabolism
• Discuss plans for delivery, including importance of in-hospital monitoring for babies exposed to antidepressants in utero
• Begin discussion of feeding choices, e.g., breast milk, formula, and combination
• Coordinate with Ob/Gyn
• Coordinate with therapist
Third trimester
• Review choices about medication during pregnancy
– Provide updates about any new data since last discussion
– Review risk of neonatal abstinence syndrome (NAS)
• Monitor depressive symptoms, and adjust dose as needed; do not lower dose to prevent NAS
• Review plans for delivery
• Provide psychoeducation about postpartum depression to both the patient and partner
• Continue discussion of feeding choices, and make plan for protecting mother's sleep after delivery (e.g., sharing feedings, night nurse, etc.)
• Encourage patient to meet with pediatrician, especially if she is planning to take medication while breastfeeding
• Discuss social supports after delivery, and help patient make plans to involve supports
• Discuss plans for return to work, including childcare options

Table 13.2 (continued)

• Coordinate with Ob/Gyn
• Coordinate with therapist
Postpartum
• Meet 1–2 weeks after delivery
• Review delivery, complications, and baby's APGAR scores
• Monitor depressive symptoms and adjust medication dose as needed
• Discuss adjustment to motherhood and assess bonding with baby
• Discuss feeding and provide support for whatever mother chooses (breastfeeding or formula)
• Evaluate sleep and review plans for protecting mother's sleep
• Discuss supports and adjust plans for help at home
• Discuss plans for return to work, including childcare options
• Coordinate with Ob/Gyn
• Coordinate with therapist

Table 13.3 Pharmacologic treatment of perinatal depression: guidelines and considerations

1. The best time to devise a treatment plan in women with histories of depression is before they conceive
2. Take care to decipher the data regarding possible medications in pregnancy or the postpartum, and explain the information to the patient and preferably also her partner
3. In general, unless there are clear adverse effects for the patient or her baby, use the medication that has worked best in the past
4. When possible, choose the medication that has the most credible safety and tolerability data
5. Although not always possible, monotherapy is preferable to polypharmacy
6. Use the lowest effective dose. Do not compromise efficacy in order to adhere to a low dose
7. Monitor the patient frequently through pregnancy and the postpartum, adjusting the dose as needed clinically. Remember that for some medications, dose adjustments may be needed due to hormonally influenced antidepressant metabolism, drug interactions, or changes in extracellular volume
8. Encourage the patient to try to get as much uninterrupted sleep as possible, as this is a factor that often influences antidepressant efficacy
9. Encourage psychotherapy, as this often provides benefit to the depressed patient who is being treated with medication. If needed, couples' therapy may be helpful as well
10. Educate the patient about treatment options with regard to breastfeeding: exclusive breastfeeding, supplementing with formula, exclusive formula feeding, etc. Explain that while most antidepressants are not contraindicated in breastfeeding, sleep is often compromised when nursing, particularly if the patient is also pumping
11. Consider hospitalization if the patient is seriously impaired, suicidal, or a threat to others, including her baby

In general, monotherapy is preferred, and dosages should be kept at the minimum necessary to promote ongoing mood stability and normal functioning. The goal is to treat with the fewest number of medications at the minimum *effective* dose. Treatment needs may also change over time, since pharmacokinetic changes during pregnancy may lead to alterations in drug or metabolite levels, with potential

need for dosing adjustments [28]. If new literature emerges during the course of a pregnancy, it should be carefully interpreted and shared with the patient.

13.5.2 Safety Profile

The safety profile of antidepressants in pregnancy is outlined in Chap. 5. While there are no randomized placebo-controlled trials of antidepressants in pregnant women, registry data does provide some evidence-based guidance. There is more data available for serotonin reuptake inhibitors (SSRIs) than other antidepressants during pregnancy, and these agents are therefore generally considered first-line treatment [29]. While serotonin-norepinephrine reuptake inhibitors (SNRIs) are less well studied than SSRIs, they have increasing data associated with their use and may be a viable alternative, particularly when a patient has previously responded well to these agents. Tricyclic antidepressants have a long history of use in pregnancy and may be a reasonable choice when a patient has failed a newer medication or has a history of response to a TCA. The NICE guidelines (last updated 2017 [30]) recommend treatment with an SSRI, SNRI, or TCA.

While newer antidepressants may be touted as having fewer side effects than their older counterparts, there is generally little to no literature regarding their use in pregnancy. Unless a woman has done poorly on several better-studied treatments, there is little justification for using a medication about which we have no information.

13.5.3 Symptom Profile

For the medication-naïve patient, symptom profile should guide the choice of antidepressant. For example, if a patient is particularly agitated or suffering from insomnia, a more sedating antidepressant is a reasonable first choice. If the patient has an anergic depression, a more activating antidepressant should be considered.

13.5.4 History of Response to Particular Medications

An important factor when recommending a medication during pregnancy is a patient's own history of medication response. Since the past is generally predictive, restarting a medication that was previously effective is the most rapid and direct way to achieve remission. If the medication previously used is one with minimal data in pregnancy, it is worth considering a trial of a more-studied medication, for example, an SSRI. On the other hand, a trial with a new SSRI in a patient who has previously failed to respond to another SSRI may only prolong the patient's depression. Ideally, any medication change should take place prior to pregnancy, since changing medications during pregnancy results in multiple exposures. Thus, for the younger woman (e.g., less than 35 years old, who is hoping to become pregnant, and

for whom there is time to try another medication), a trial of a more-studied medication such as an SSRI is a reasonable approach. However, unlike the younger patient, the woman over 35, perhaps with a history of infertility or multiple pregnancy losses, may not have reproductive time ahead to experiment with a new medication. In these cases, it is prudent to continue with a medication that has been effective but may have somewhat less data to support its use in pregnancy.

13.5.5 Dosing

Pharmacokinetic changes during pregnancy can lead to changing drug or metabolite levels, and it is therefore possible that a dose that was previously effective will no longer work for a particular patient. Since there are no dosing parameters specific to pregnancy, standard depression dosing should be used as a starting point, with adjustments made based on clinical response. A woman should be seen frequently during pregnancy and should be made aware early in treatment that dosing may need to be increased. While previous clinical guidelines recommended decreasing the dose of antidepressants in the third trimester in order to mitigate the risk of neonatal abstinence syndrome (NAS), that strategy is no longer recommended for two reasons: (1) decreasing the dose prior to delivery leaves a woman undertreated just as she enters the vulnerable postpartum period, and (2) research studies have not demonstrated a decrease in NAS with lower antidepressant doses [31, 32].

13.6 Treatment of Postpartum Depression

The postpartum is a vulnerable time for women, particularly if they have histories of depression either before or during pregnancy. Postpartum depressed women often struggle with meeting the needs of their babies and other children while taking care of their own mental health. Like depressed pregnant women, postpartum depressed women frequently feel conflicted about the "best" treatment regimen to treat their depression while safeguarding the health of their babies.

As during pregnancy, the goal of the treating clinician should be to help new mothers accept that although the information about treatment options is necessarily limited by literature that is compromised by confounders and is constantly changing, of paramount importance is the need to recover from depression in order to maximize the best possible outcome for the mother, baby, and other family members. While the information regarding treatment options is limited, it is sufficient to allow clinicians to sort through treatment options with their patients and to facilitate thoughtful decisions that will enable a healthy and gratifying outcome for new mothers and their babies.

As discussed earlier in the chapter (see Sect. 13.3), the treatment of postpartum depression must include a thorough assessment of both suicide risk and risk of infanticide. If a mother is deemed at high risk of harming herself or her baby, she should be hospitalized, ideally in a setting where she can continue to have contact

with her infant while being supported in her recovery. It is also important to screen depressed mothers for features associated with bipolar disorder (e.g., history of mania/hypomania, family history of bipolar disorder, switches on antidepressants, early onset of mood symptoms, etc.), since postpartum depression can sometimes be the index episode of bipolar illness [33].

In general, if a woman has responded well to a particular medication in the past (including during pregnancy), that medication should be the starting point. SSRIs are the best studied and most frequently used medications for postpartum depression. There are very few randomized controlled trials of antidepressants for postpartum depression. Pooled estimates from a 2014 Cochrane Review found that SSRIs were significantly more effective than placebo in treating postnatal depression; however, the sample sizes were small, and the quality of the evidence was deemed low [34]. Medication dose should be increased to an effective dose as quickly as tolerated; caution should be exercised not to underdose a woman because she is nursing.

Most postpartum women are sleep-deprived due to their babies' feeding schedules, and lack of sleep is magnified significantly when mothers choose to breastfeed (often pumping to augment milk production). Even if they are totally exhausted and suffer from increasing debilitating depression, many women feel guilty even thinking about limiting or discontinuing breastfeeding. For those depressed women who find breastfeeding to be fulfilling, they worry about exposing their babies to psychiatric medications.

From a clinical standpoint, decisions about breastfeeding should be made with attention not only to medication safety but also to the impact on maternal mental health. If a woman finds breastfeeding to be fulfilling, she should be encouraged to continue. However, if breastfeeding worsens her depression or interferes with her ability to care for herself and her baby, she should be given permission to stop.

Most antidepressants are considered compatible with breastfeeding, with weight-adjusted maternal dose delivered through breast milk falling under the 10% threshold regarded as clinically relevant. As during pregnancy, the SSRIs are better studied during lactation than other antidepressants, and sertraline is generally considered the preferred agent due to its minimal passage into breast milk [35]. Please see Chap. 6 for details about particular antidepressants during lactation.

When discussing options regarding treatment of postpartum depression, it is essential to address the importance of sleep. Fatigue during the postpartum period worsens depressive symptoms, and depression contributes to further insomnia [36]. Even if a woman is breastfeeding, it can be helpful to have another person (partner, relative, night nurse) assist with night feeding, in order to allow the new mother to get one uninterrupted stretch of sleep. Depression is extremely challenging to treat when a woman is significantly sleep-deprived, and adequate sleep often goes a long way toward the successful treatment of postpartum depression. Treatment of postpartum depression should also address comorbid anxiety, which is common in new mothers and can impact both sleep and daily functioning.

While most women can be treated with psychotherapy and antidepressants, some postpartum depression is not responsive to standard treatment. Hormonal therapies

Table 13.4 Expert recommendations based on scientific evidence and clinical experience

The overall goal of treatment is to maximize maternal wellness, since maternal well-being is intimately tied to infant and family well-being
Decisions about medication should be made collaboratively, ideally involving the patient, her partner, obstetrician, and psychiatrist in the decision-making process
The best antidepressant during pregnancy is the one that works for the patient
All else being equal, when treating antenatal depression, it is better to choose a medication that has more data behind its use
Treatment during pregnancy should be with the fewest possible medications at the lowest *effective* dose
In the postpartum period, addressing sleep deprivation and protecting maternal sleep are an essential component of treating depression
Decisions about breastfeeding should be made with attention not only to medication safety but also to the impact on maternal mental health

are an emerging treatment option. Brexanolone is an intravenous formulation of allopregnanolone—a positive allosteric modulator of γ-aminobutyric acid ($GABA_A$) receptors—that is showing promise for the treatment of severe postpartum depression. A double-blind randomized phase 2 clinical trial of 21 women demonstrated significant improvement in symptoms 60 h after medication infusion without any adverse side effects [37], and phase 3 trials of severe and moderate PPD demonstrated similar results [38].

13.7 Conclusion

It is important to remind women that perinatal depression is treatable. While a subset of women do go on to experience chronic depression, a large proportion recover. Ongoing monitoring, discussion, and collaboration can significantly improve the experience of early motherhood for women with depression (Table 13.4).

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Bipolar Disorder

14

Michael Thomson and Verinder Sharma

14.1 Introduction

Managing bipolar disorder (BD) during the perinatal period involves a complex balancing of the risks associated with the maternal illness versus the risks that medication exposure can pose to the foetus or neonate. Factors that further complicate management include a lack of consensus guidelines, differing patient priorities, little consistency in clinician practices and the exclusion of pregnant and postpartum women from most clinical studies. To date, no randomized controlled trials (RCTs) have investigated the pharmacological management of BD in pregnant or postpartum women. BD has been associated with an increased risk of adverse obstetrical outcomes, some of which are independent of medication exposure [1].

Although the prevalence of BD in obstetrics populations has not been well established, the lifetime prevalence of BD is 1.0% for type I, 1.4% for type II and 2.4% for BD not otherwise specified [2]. Given its relatively high prevalence and its propensity for affecting women of reproductive ages [3], the knowledge on its management is imperative for clinicians providing care to women. The best estimate of BD in an obstetrics population may be from a screening study which identified that 5.1% of prenatal women from a nonpsychiatric population were deemed high risk for BD using the Mood Disorder Questionnaire (MDQ) [4].

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14.2 Identifying Perinatal Bipolar Disorder

BD is often a difficult clinical diagnosis to establish and misdiagnosis is frequent. Symptomatically the illness can overlap with multiple other psychiatric disorders including major depressive disorder (MDD), psychotic disorders, substance use disorders and personality disorders among others. Additionally, underlying medical concerns such as hypothyroidism can also present with psychiatric manifestations [5]. The first presentation of BD is usually that of a major depressive episode (MDE) which can make the illness very difficult to distinguish from MDD. Based on the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*, BD type I or II cannot be diagnosed until a manic or hypomanic episode has occurred [6]. Many patients have the illness for multiple years prior to correct diagnosis [7]. Although universal screening for perinatal depression has been recommended by the American College of Obstetricians and Gynecologists [8], this generally has not included screening for BD. In both research studies and in clinical practice, the most commonly used screening tool has been the Edinburgh Postnatal Depression Scale. This tool has a sensitivity ranging from 67% to 100% and a specificity ranging from 87% to 100% in detecting postpartum depression [9]. Another easy-to-use questionnaire, the MDQ, has been validated by Sharma and Xie for the screening of BD in the postpartum period. They demonstrated a sensitivity of 87.72% and a specificity of 85.29% for the identification of BD in postpartum women when the supplementary questions on the MDQ were excluded [10]. This tool has not yet been validated for the antenatal population.

First presentations of BD are usually MDEs which can be very difficult to distinguish from an MDD. Atypical symptoms of depression can be suggestive of BD, yet these are also frequently observed in MDD [11]. As BD is highly heritable, obtaining a thorough family history of psychiatric disorders is vital including specific questioning on family history of BD and perinatal psychiatric concerns [12].

It is increasingly being recognized that the postpartum period is a high-risk time for the first onset of BD [13–16]. As such, clinicians should be vigilant in screening for the illness in postpartum women presenting with symptoms of a mood disorder. Although MDD and bipolar depression can be very difficult to differentiate, features which can be suggestive of bipolar depression are the onset of depressive symptoms within the first 2 weeks postpartum, a family history of BD and atypical depressive symptoms.

14.3 The Complexity of Bipolar Disorder Management During Pregnancy

Unfortunately, all medications used in the treatment of BD have the potential to cause significant harm to both the mother and her baby. Some of the commonly used mood stabilizing medications, e.g. valproate and carbamazepine, are well known to be teratogens [17]. However, untreated maternal illness can also pose large risks

including suicide, substance abuse and low compliance with prenatal care. In many cases these risks outweigh the risks of medication exposure. As the risks and benefits must be weighed on a case-by-case basis, it has been very difficult to establish general management guidelines for this population. Additionally, the woman's preferences in treatment are a paramount factor which must be factored into treatment decisions. Some women decide that preventing a relapse or optimizing control of their mood symptoms is their primary concern and in doing so are willing to tolerate a higher risk of foetal medication exposure. Many others decide that foetal safety is their top priority and are willing to accept an increased risk of BD relapse to minimize foetal exposure to medications.

Where possible, the use of medications during the perinatal period should be limited to monotherapy. Women with BD often have complex medication regiments prior to conception, especially in cases of more severe or treatment-resistant illness. Studies of foetal risk associated with mood stabilizer polytherapy are lacking. However, one study showed higher rates of congenital anomalies with polytherapy compared to monotherapy for the treatment of epilepsy [18]. Another study showed higher rates of adverse outcomes for both the mother and foetus when antipsychotics were combined with other psychotropic medications compared to antipsychotic monotherapy [19]. Another factor contributing to the complexity of antenatal BD management has been a lack of consistency in the findings of adverse foetal outcomes attributed to different mood stabilizing medications. Most systematic reviews and meta-analyses which have analysed the foetal risks associated with antipsychotics have looked at the medications as a group rather than separating out data for individual antipsychotics [20]. Studies of foetal risk using information from population-based databases often have significant confounding factors which are co-morbid to the psychiatric disorder being treated such as higher rates of substance abuse, poorer physical health and poorer access to prenatal care. BD itself may have a teratogenic risk as it has been associated with higher rates of microcephaly and neonatal hypoglycaemia in offspring [1]. Yet, overall understanding of the risks that the illness itself poses to pregnancy is not well established.

14.4 Risks of Untreated Bipolar Disorder

The risks associated with untreated maternal BD during pregnancy have not been well established. Multiple studies have associated untreated maternal depression with adverse markers of foetal health and adverse pregnancy outcomes [21, 22]. However, these findings predominately relate to major depressive disorder and may not be applicable to BD. A single population-based study compared pregnancy outcomes from women with untreated BD to women with treated BD and women without BD. This study demonstrated increased rates of neonatal microcephaly, neonatal hypoglycaemia, preterm birth, small-for-gestational-age infants and induced or planned caesarean section in women with BD even when the illness was untreated [1].

Women with BD who remain medication-free during the postpartum period experience significantly higher relapse rates compared to women taking mood stabilizers during this time [23].

14.5 Preconception Planning in Bipolar Disorder

In ideal situations, women with BD are identified early and stabilized on medication for a prolonged period prior to conception. This notion was supported by research of Viguera et al. [24] who demonstrated a decreased risk of relapse in women with BD who had a prolonged period of stability before pregnancy. However, the length of time considered to be a prolonged period was not defined in the study. Women who are family planning often request consultation with their healthcare providers to discuss the implications of their medication on pregnancy, or they inquire about the pregnancy risks associated with a medication prior to starting it. These are opportune times for clinicians to provide education on the risks and benefits of psychotropic medications and to lay the groundwork for medication management should a pregnancy occur. Tapering of a medication is easier to trial before pregnancy occurs as foetal exposure is not an ongoing concern; it is easier to attempt a slow taper, and medications can quickly be reinstated should a relapse occur. However, given that 50% of all pregnancies are unplanned and this increases to 2/3 in women with BD [25], this opportunity will often not be available. Unplanned pregnancies have been associated with significantly higher rates of relapse [24, 26], which is likely multifactorial with psychosocial contributions in addition to women abruptly discontinuing medications upon learning they are pregnant.

Preconception counselling should begin by obtaining a thorough psychiatric history. Important information to obtain includes the number of prior mood episodes, severity of past episodes, duration of euthymic periods between episodes, past response to medications, family psychiatric history, history of suicidality and history of psychosis [27]. Completing a thorough psychiatric history helps with estimating both the risk of a mood episode relapse occurring and the potential severity should this happen. Family history of BD, postpartum mood disorders and postpartum psychosis should be elicited as these have been associated with a risk of postpartum mood episodes [27]. The woman should be counselled on the foetal risks associated with her psychotropic medications, advised of any alternative medications which may be safer and educated on the risk of a mood episode relapse during the perinatal period. It is also important to identify co-morbid psychiatric disorders as these are usually the rule rather than the exception, in BD. The treatment of co-morbid disorders must be taken into consideration as they bring additional complexity into treatment decisions, e.g. different medications or options for therapy. There has been little research on the prevalence of co-morbid psychiatric disorders in perinatal women with BD. However, one naturalistic study of women with BD identified lifetime co-morbidity rates of 51% for anxiety disorders, 11% for alcohol abuse and 10% for cannabis use disorder [28]. Identification and treatment of

co-morbidities may reduce the risk of a BD relapse and reduce maternal morbidity. If present, obesity, substance use disorders and smoking should all be addressed as they are more prevalent in individuals with BD [29] and are associated with a higher risk of adverse maternal and neonatal outcomes.

Population-based studies have identified that discontinuation of psychotropic medication is common in women who become pregnant. A recent Canadian study identified that 16.2% of women filled at least one prescription for psychotropic medication in the 3 months before pregnancy. This number decreased to 6.0% during pregnancy and was 9.5% in the first 3 months postpartum. The study also identified an increase in the use of psychotropic medications before, during and after pregnancy from 2003 to 2013. Women who were taking an antiepileptic medication were more likely to continue their medication throughout pregnancy (18.1%), but this may largely reflect treatment for epilepsy rather than BD. Only 7.8% of women taking antipsychotic medications continued them throughout pregnancy, and 29.0% had intermittent use [30]. Should discontinuation of mood stabilizing medications be attempted prior to conception or during pregnancy, it is best done under medical supervision so that relapses can be quickly identified and addressed. Tapering of medications, rather than abrupt discontinuation, has been associated with a much lower risk of relapse during pregnancy [24]. Monitoring mood states without the use of medication may be appropriate in women who have had a mild lifetime illness course (e.g. no history of suicide attempts or psychosis and a historical good response to treatment). Another option that can be discussed is the discontinuation or tapering of medications during the first trimester with resumption in the second or third trimesters. This theoretically reduces foetal exposure to medications during the predominant periods of organogenesis.

As the severity of the past illness course increases (e.g. a history of suicide attempts, psychotic features and only partial response to medications), the estimated risk of a relapse also increases. These women may require maintenance treatment to reduce the risk of a relapse and to reduce the severity should one occur. Close follow-up is required if a woman with a history of severe illness attempts medication discontinuation. Where possible, family members should be involved in the treatment process, educated on signs of relapse and made aware of how medical care can be accessed should a relapse occur. When reviewing psychotropic medications during pregnancy and the preconceptual period, all the woman's psychotropic medications should be scrutinized. Women with BD are frequently prescribed antidepressant medications despite their role in treatment of the disorder being controversial [29, 31–33]. A naturalistic study of pregnant women with BD identified that 9% of women with both BD I and BD II were treated either with antidepressant monotherapy or with antidepressants combined with other medications that were not guideline-concordant [28]. The use of antidepressants in pregnant women with BD is a robust predictor of depression relapse during the pregnancy [24]. Clinicians must be aware of the potential foetal safety concerns posed by antidepressant medications and be mindful that these medications may increase the risk of relapses, especially if they are unopposed following the discontinuation of mood stabilizing medications [24].

14.6 Management of Antenatal Bipolar Disorder

14.6.1 Acute Treatment

Whether or not to initiate medications in the treatment of acute mood episodes will depend on the severity of the episode and the woman's preferences for treatment. In milder cases, a wait-and-watch approach may be appropriate. In more severe cases, urgent intervention is often required which may include hospitalization. Severe cases generally include those with suicidality, psychosis or significant functional impairment. There have been no clinical trials on the treatment of acute BD episodes in pregnancy. As such, it is reasonable to use best-evidence guidelines from non-perinatal populations with additional considerations given to medication pregnancy safety profiles. Preference is usually given to medications that have previously been beneficial in treating the woman's illness; however, this should be balanced with the pregnancy safety profile of the medication. When the previously used medication is associated with significant foetal risk (e.g. valproate), it may be best to trial a medication with a better pregnancy safety profile despite the mother's response to this alternative medication potentially being unknown. Detailed discussion on the safety of different mood stabilizing agents including lithium, antiepileptic medications and antipsychotics are covered in detail in Chaps. 7 and 9.

Most antenatal bipolar relapses that occur are depressive episodes [34]. Guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) indicate that both lamotrigine and quetiapine are first-line medications for the acute treatment of bipolar depression [29]. Although not without risk, these medications are thought to be among the safest mood stabilizers for use in pregnancy [35, 36]. If a relapse occurs despite the woman taking maintenance medications, then dosage optimization should be attempted before using augmenting medications. In situations where the maximum dose has been reached or there are intolerable side effects, then augmentation can be considered. However, studies have identified additive, and potentially synergistic, increases in the risk of congenital anomalies with polypharmacy [18, 19]. Additionally, there are no studies which have established efficacy for any augmenting agents in this population.

Any antidepressant medication that pregnant women with BD are taking should be given scrutiny. The use of antidepressant medications in women with BD is common [28], and their use in treating the disorder has been controversial [29]. Antidepressant use was shown to be a robust predictor of BD relapse in a study by Viguera et al. in 2007. However, the use of antidepressants in this study may have been a marker of more severe maternal illness [24]. Clinicians should be mindful that the observed effects of antidepressants may change if mood stabilizing medications are discontinued and the antidepressants become unopposed. It is also important to be watchful for antidepressant withdrawal which must be differentiated from a mood disorder relapse. A thorough screening for co-morbid psychiatric disorders should be undertaken as these conditions may be benefiting from the use of antidepressants, but alternative treatment options may also be available for them.

The use of psychotherapy may be an additional treatment option. Although there is no evidence supporting the use of psychotherapy in antenatal BD, some meta-analyses have shown efficacy for its use in non-perinatal BD. The 2018 CANMAT/ISBD guidelines have recommended psychoeducation as a first-line adjunctive maintenance treatment in BD [29]. Efficacy for monotherapy with social rhythm therapy without the use of medication was suggested by a small proof-of-concept study involving 17 non-perinatal patients with acute bipolar II depression. In the study, 41% of the patients achieved ≥50% symptom reduction by 12 weeks. An additional 41% of the patients dropped out or were removed which could suggest that the response rate was even an underestimation of efficacy [37]. Psychotherapy, particularly cognitive behavioural therapy (CBT), may be very helpful for women who have a co-morbid anxiety disorder [38]. The efficacy for CBT in reducing relapse risk in non-perinatal BD was seen in one RCT [39]. A second, larger RCT found that CBT may be helpful in reducing relapse risks in non-perinatal BD patients who have had fewer mood episodes, but not in those who have had ≥12 past episodes [40].

An increasing body of research has suggested that lamotrigine may have one of the best pregnancy safety profiles among the mood stabilizing medications. Most studies have not identified an increased risk of congenital anomalies with lamotrigine use. A single study found an increased risk of oral cleft defects [41], but this was not replicated in a later meta-analysis and systematic review by Pariente et al. [36]. Lamotrigine has also been labelled as a first-line medication for both acute bipolar depression treatment and maintenance treatment in the CANMAT/ISBD guidelines [29]. Maintenance treatment efficacy with lamotrigine was demonstrated in a 2008 study by Newport et al. [42] where 30% of women taking lamotrigine had postpartum BD relapses versus 100% of women not taking mood stabilizing medications.

There are no clinical trials available to guide the management of manic or mixed episodes during pregnancy, and the existing literature is limited to case reports and case series. As such, treatment decisions largely rely on data extrapolated from studies using non-perinatal populations. Usually antenatal hypomanic episodes are monitored without pharmacological intervention to see if they remit spontaneously. Addressing psychosocial factors and attempting strategies to improve sleep are often beneficial. Should significant safety concerns or significant functional impairment arise, medications can be initiated, or if currently being used, optimized. Studies in non-perinatal patients have shown haloperidol to be among the most efficacious medications for treating acute manic episodes [43]. However, prolonged use of haloperidol may increase the risk of a depressive episode [29, 43]. Although not without risk, haloperidol has a long history of use in pregnancy, and it has not been associated with an increased risk of congenital anomalies. A study that examined a group of pregnancies exposed to haloperidol ($n = 188$) and penfluridol ($n = 27$) did not show an increased risk of congenital anomalies compared to a control group (3.4% versus 3.8%, $p = 0.787$). It should be noted that a study limited to 188 cases is likely underpowered for detecting smaller increases in the risk of congenital anomalies, especially when looking for specific anomalies. The group receiving haloperidol or penfluridol had higher rates of pregnancy termination (8.8% versus 3.8%, $p = 0.004$),

and there was a trend towards a higher rate of miscarriage, but this did not achieve statistical significance (8.8% versus 5.5%, $p = 0.105$). The rates of stillbirth (0.0% vs 0.2%, $p = 1.00$) were comparable between the antipsychotic group and control group [44]. Quetiapine is another anti-manic medication which appears to have one of the better pregnancy safety profiles. A systematic review including 443 pregnancies exposed to quetiapine in the first trimester showed a congenital anomaly rate of 3.6% (16/443) [35]. The background risk for major congenital anomalies is felt to be around 3% [45]. Another study of 54 late-stage pregnancies determined that the mean concentration of quetiapine obtained from umbilical cord blood was only 24% of the maternal concentration. This was the lowest ratio among the antipsychotics used ($n = 20$ for quetiapine) [46]. Unfortunately, studies have suggested that lamotrigine is not effective in treating mania and this medication requires slow titration given the risk of Stevens-Johnson syndrome [47]. Lamotrigine is not recommended for the treatment of mania in the CANMAT/ISBD 2018 guidelines which were developed for the general BD population [29].

14.6.2 Management of Newly Diagnosed Bipolar Disorder

Pregnancy may be the time of the first onset for a mood disorder, or it may be the time during which a BD is first recognized. This is made more likely by the significant overlap between the ages that BD generally first onsets and the reproductive years in women [3]. However, the rate of the first onset of BD during pregnancy has not been established [48]. In some cases, a new diagnosis of BD may be made when a pregnant woman is referred by her general practitioner or obstetrician for psychiatric assessment during pregnancy. The diagnosis is usually made when the clinician identifies past hypomanic or manic episodes. However, this then poses the challenge of how the psychiatric disorder should be managed during the pregnancy. In this situation, a preconceptual trial of medication is no longer an option, and starting medication poses the risk of foetal medication exposure with unknown maternal response. In cases where there are minimal concerns with respect to suicidality and functional impairment, a wait-and-watch approach may be appropriate. This allows additional time for diagnostic clarification, and it allows the pregnancy to progress further before foetal medication exposure occurs. However, urgent intervention and hospitalization are usually required in situations where there is suicidality, psychosis or significant functional impairment. When a wait-and-watch approach is pursued, it is important to educate the woman and her supports about the possibility for worsening mood symptoms and to discuss how care can urgently be accessed should this occur.

14.6.3 Maintenance Treatment

The goals of maintenance treatment are to reduce the risk of a relapse during pregnancy as well as in the postpartum period. In predicting the risk of an antenatal BD relapse, it is important to understand the course of the illness during pregnancy. In

the past it was believed that pregnancy was protective against mental illness. It is now understood that the influences of pregnancy on mental illness are not clear-cut and there is currently a lack of consensus regarding the effects of pregnancy on BD. Sharma and Pope [48] analysed studies of BD illness course in pregnancy and concluded that there is evidence from nonclinical samples, retrospective studies and studies of hospitalization rates which are suggestive of a protective effect of pregnancy on BD. However, they also note that studies have shown a high relapse rate during pregnancy when mood stabilizing medications were discontinued. In a retrospective study by Viguera et al. [24], women who discontinued lithium during pregnancy had comparable relapse rates to non-pregnant women who discontinued lithium (52% versus 58%, respectively) when both groups were followed over a period of 40 weeks. The women in both groups relapsed more frequently than they did in the year prior to lithium discontinuation. A similar study by Grof et al. [49] compared the risk of relapse in 28 pregnant women against 33 non-pregnant women. All the women had BD I and were responsive to lithium. Relapses occurred less frequently in the pregnant group compared to the non-pregnant group. Women in the pregnant group had fewer relapses during their pregnancy than they did in the 9 months preceding the pregnancy. Additionally, most of the relapses that occurred during pregnancy took place in the last 5 weeks of gestation. These studies suggest that pregnancy may have either a neutral or protective effect on the course of BD. However, the results of a study done in a lithium-responsive antenatal BD I population are not necessarily applicable to all cases of antenatal BD. A retrospective study by Viguera et al. analysed the risk of mood episodes in 1162 women comprising 2252 pregnancies. Of the women enrolled, 283 had BD I and 338 had BD II. The risk of a BD relapse during pregnancy was 22.7% [34]. Another study by Viguera et al. [24] compared the risk of relapse during pregnancy in women who remained on mood stabilizing medications versus those who discontinued them. The group that remained on the medications had a relapse rate of 37.0% versus 85.5% in the group that discontinued the medications. This 37.0% was further broken down to 18.5% of the women who experienced depressive episodes, 25.9% who had hypomanic episodes and 7.4% who had manic episodes. No mixed episodes were identified in the women who continued to take maintenance medications. The relapse rate for the group of women who discontinued medications was much higher at 85.5%. The time to relapse was also four times longer in the group that continued mood stabilizing medications (>40 weeks versus 9 weeks). However, there were significant confounding factors between the groups which must be considered. Women from the group that discontinued the medications were more likely to be taking multiple psychotropic medications, had a longer duration of illness, were more likely to have illness onset before age 15 and had significantly higher rates of rapid cycling. All of these are indicators of increased illness severity. They were also more likely to be taking antidepressant medications (66.1% versus 18.5%), to have an unplanned pregnancy and to be diagnosed with BD II which are all factors associated with higher relapse rates during pregnancy.

Individualized assessments of the risks and benefits of medication use must be performed when making decisions on maintenance treatment in antenatal BD. It has

been well established that discontinuing maintenance treatment is associated with an increased risk of relapse during pregnancy and an even higher risk for postpartum relapse. Yet, there are risks to both the mother and the foetus with medication exposure. Obtaining a thorough psychiatric history helps to estimate the woman's risk of having a relapse and to predict the potential severity should this happen. This risk assessment should be discussed with the woman, and her views on the use of medication should be inquired about. Many pregnant women prioritize the minimization of foetal medication exposure and are willing to accept a higher risk of relapse in order to do so. In cases where the illness has been stable for a minimum of 4–6 months and the woman is considered to be at low risk for relapse, discontinuing medication with symptom monitoring may be the overall safest option [29]. This approach minimizes foetal exposure but does so at the cost of increasing the risk of a relapse. Where possible, family members and others involved should be engaged in the treatment planning so that they can provide additional support to the woman if needed and assist her in obtaining medical care should decompensation occur. In cases where complete discontinuation of medications poses too great of a risk or there are multiple psychotropic medications being used, a strategy involving the selective tapering of medications may be appropriate. In this situation, medications which pose the greatest foetal risk or those which have been the least beneficial should be considered first. Another strategy commonly used in the treatment of antenatal BD is the tapering or discontinuation of mood stabilizing medications during the first trimester with a plan to restart them in the second or third trimesters. The main benefit of this strategy is that foetal medication exposure is reduced during the time of organogenesis. This allows for prophylactic mood stabilizing medications to be reinitiated before the postpartum period which is the highest-risk time for relapse. However, a downside is that antenatal BD relapses may have a propensity for the first trimester. In the Viguera et al. [24] study, 47% of antenatal relapses occurred during the first trimester. However, this notion conflicts with the Grof et al. [49] study where most of the women who relapsed following lithium discontinuation did so in the late third trimester. Another factor of consideration is that a woman may not become aware of the pregnancy until after the period of highest risk for teratogenicity has already occurred.

There is a dearth of research looking at BD maintenance treatment during pregnancy. Most of the research that does exist has analysed the risk of relapse in women who continue versus those who discontinue mood stabilizing medications. No RCTs have looked at this, and studies comparing the efficacy of different medications have been minimal. Most of the existing studies that have been done have used lithium. These studies have shown lithium to be efficacious in reducing the risk of mood episode relapses both during pregnancy and in the postpartum [24, 50, 51]. Lithium has also been recommended as a first-line treatment for bipolar depression, maintenance treatment and mania in the non-perinatal BD population [29]. However, the safety of lithium during pregnancy has not been firmly established, and there are conflicting opinions on its use. The National Institute for Health and Care Excellence (NICE) recommended that antipsychotic medications be used preferentially over lithium in women with BD who are pregnant or planning on becoming pregnant. It

further advises that lithium be discontinued with consideration of using antipsychotics if women become pregnant while on lithium or that lithium be discontinued and then restarted in the second trimester [52]. The most recent large cohort study was done by Patorno et al. [53]. This study looked at 1,325,563 infants of which 663 were exposed to lithium in the first trimester. The rate of cardiac malformations in the lithium-exposed infants was 2.41% compared to 1.15% in nonexposed infants and 1.39% in infants exposed to lamotrigine. After adjustment they found a risk ratio for cardiac malformations of 1.11 with daily doses less than 600 mg, 1.60 for daily doses between 601 and 900 mg and 3.22 for daily doses greater than 900 mg. The relative risk of malformations overall was 1.37 (95% CI 1.29–2.40) in infants exposed to lithium versus unexposed infants after adjustment.

If lithium is used in pregnancy, close monitoring of serum levels is required. Lithium excretion increases as the glomerular filtration rate increases. As such, dosage increases may be required to prevent symptom relapse. A recent study by Wesseloo et al. [54] monitored lithium levels obtained from 113 pregnancies. Compared to the preconception baseline lithium levels, there were changes of −24% in the first trimester, −36% in the second trimester and −21% in the third trimester, and there was an increase in lithium levels by 9% in the postpartum. This suggests that lithium clearance is highest during the second trimester and that lithium levels can increase quickly in the postpartum if not closely monitored. The authors recommended monitoring lithium levels every 3 weeks until 34 weeks of gestation and then weekly until delivery. Given the risk of lithium toxicity that can occur postpartum, especially if doses were increased during pregnancy, the authors have recommended that lithium levels be checked twice weekly for the first 2 postpartum weeks. They also recommended using a higher target serum lithium level (≥0.8 mmol/L) in the first postpartum month as this is the time of highest risk for relapse. There are mixed opinions on how lithium should be dosed in the days prior to delivery. Some experts have recommended holding lithium for 1–3 days as higher serum lithium levels have been associated with adverse neonatal effects. Others have felt that holding lithium prior to delivery is unnecessary if the woman remains well hydrated and that doing so may increase the risk of a postpartum relapse. Anti-inflammatory medications should be avoided while taking lithium as they can increase the risk of toxicity.

Lamotrigine has shown efficacy in preventing antenatal BD relapses in small studies. Newport et al. [42] followed a group of 26 women who were euthymic at conception and assessed for major depressive, hypomanic or manic episodes during pregnancy. There were significantly lower rates of relapse in the women maintained on lamotrigine (30%) versus the group that discontinued mood stabilizing medications which had a 100% relapse rate. Additionally, the time to 25% relapse was 14 times longer in the women who took lamotrigine throughout pregnancy (28.0 versus 2.0 weeks). Lamotrigine is generally thought to have a favourable pregnancy safety profile when compared to other mood stabilizing medications (further discussed in Chaps. 7 and 9). A recent systematic review and meta-analysis by Pariente et al. [36] did not find an increased risk of congenital malformations in foetuses exposed to lamotrigine when compared to a disease-matched control group (OR 1.15, 95% CI

0.62–2.16) and a control group without mood stabilizing medication exposure (OR 1.25, 95% CI 0.89–1.74). Additionally, they did not detect increased rates of preterm delivery, spontaneous abortion, stillbirth or small-for-gestational-age neonates after lamotrigine exposure, but these outcomes were not meta-analysed. Lamotrigine may require dosage titration throughout pregnancy to maintain a euthymic state as clearance of the medication increases. A study of serum lamotrigine concentrations in 14 pregnant women showed a progressive increase in lamotrigine clearance until it peaked at 32 weeks and then declined. The peak clearance was 330% of baseline [55]. Similar to lithium, abrupt dosage reductions may be required immediately following delivery to avoid developing toxicity.

A single-case study by Uguz [56] has suggested that both quetiapine and olanzapine may be effective in the maintenance treatment of antenatal BD. He reported on six cases where low-dose olanzapine was used (5–10 mg) without any antenatal relapses occurring. He also reported on two cases of maintenance treatment with quetiapine, one of which experienced a relapse that resolved with reinstating the pre-pregnancy medications. Detailed discussion of the safety of antipsychotics in pregnancy is provided in Chap. 7.

14.6.4 Prophylaxis Against Postpartum Relapses in Bipolar Disorder

Prophylactic treatment against postpartum BD episodes cannot be entirely separated from prophylactic treatment of antenatal episodes. As with other areas of management in perinatal BD, studies of management in the early postpartum period are few. A meta-analysis by Wesseloo et al. [23] clearly showed that women who remain on mood stabilizing medications during pregnancy have a lower rate of postpartum relapse (23% versus 66%). Women taking prophylactic medications in the postpartum also had a significantly lower relapse rate at 29% (CI 16–47%). Of these women, 22 initiated prophylactic medications in the immediate postpartum and 38 were taking medication during pregnancy. The authors were unable to determine the relapse rate in women who initiated mood stabilizing medications in the postpartum, but they reported on previous studies that analysed this. One study showed a relapse rate of 30% (3/10 women) with immediate postpartum prophylaxis [57]. Another study had a relapse rate of 14% (3/21) in women who initiated postpartum lithium [58]. In a third study, a group of 20 women who initiated prophylactic lithium in the postpartum had no relapses, whereas 44% (4/9) of the women who remained medication-free did [50]. The results of these studies suggest that the risk of experiencing a postpartum BD relapse may be greatly reduced when prophylactic medication is started in the immediate postpartum even when women remain medication-free during pregnancy.

A small study by Sharma et al. suggested that there may be benefit from starting olanzapine in the immediate postpartum for women with BD who remain medication-free in pregnancy. In the open-label study, a group of 11 women treated with olanzapine, with or without a mood stabilizer, had a much lower relapse rate

than 14 comparison women who were treated with a mood stabilizer, an antidepressant or no medication (18.2% versus 57.1%). Only three of the 11 women in the olanzapine group initiated the medication before parturition [59].

A single study has compared the efficacy of two different mood stabilizing agents (lithium and lamotrigine) in preventing relapses requiring psychiatric hospitalization. In this study there were no statistical differences in the hospitalization rates between the groups with 7.3% of those taking lamotrigine hospitalized and 15.3% in those taking lithium (adjusted OR 0.83, 95% CI 0.22–3.14) [60].

14.7 Management of Bipolar Mood Disorder Episodes in the Postpartum Period

There is an increasing evidence base indicating that the postpartum period is a time of high risk for both first presentations and relapses of BD. Depressive episodes are the most common form of relapse that occur, but hypomanic, manic and mixed episodes also occur at increased frequencies [34]. There have only been two open-label studies of the acute treatment for postpartum bipolar depression, both of which used quetiapine. The study by Sharma et al. involved 18 postpartum women with BD. All the women had an onset of depression within the first 4 weeks postpartum. After treatment with quetiapine for 8 weeks (median dose was only 75 mg), 83% of the women were reported as "much improved" or "very much improved" [61]. A second study by Misri et al. [62] included 26 women and used doses of quetiapine XR between 50 and 300 mg. Remission of depression was achieved at an average quetiapine XR dose of 137.5 mg, and sleep restoration occurred at 114.3 mg. At the 14-week point, 86.7% of the women were asymptomatic. Although these two small studies using quetiapine are promising, overall there is a dearth of evidence to guide the management of postpartum BD. Given this, it is reasonable to extrapolate from guidelines which have been created for the non-perinatal population. In situations where the women have opted not to breastfeed, the guidelines can be followed as they would for non-postpartum women [29]. Alternatively, when women are breastfeeding, the risks of different medications to the breastfeeding infant must be given careful consideration. Detailed discussion of mood stabilizing medications during breastfeeding can be found in Chaps. 8 and 10.

14.8 Management of Postpartum Psychosis

Postpartum psychosis is a psychiatric emergency which occurs in 0.89–2.60/1000 postpartum women [63]. These episodes most frequently occur within the first weeks postpartum. A study of 130 women with postpartum psychosis admitted to a mother-baby inpatient unit reported that the most common symptoms were irritability (73%), abnormal thought content (72%) and anxiety (71%). Suicidal ideation was present in 19% of the women and infanticidal ideation in 8%. The most common presentation was depressive (41%). A manic profile was seen in 1/3 of the

women, and 25% had an atypical presentation [64]. Psychiatric hospitalization is generally required as there is usually significant functional impairment in addition to greatly increased risks for suicide and infanticide [65, 66]. Treatment usually involves antipsychotic medications but can also involve antiepileptics, benzodiazepines or electroconvulsive therapy (ECT) [67]. Previous studies on prophylaxis against postpartum psychosis have predominately used lithium and shown this medication to be efficacious [50]. A small study by Sharma et al. [59] suggested efficacy for olanzapine in preventing postpartum psychosis in women with BD.

To date, there have not been any RCTs in the treatment of postpartum psychosis. Most of the literature available is limited to case studies and case reports which have used various mood stabilizing medications. The largest study completed was by Bergink et al. [68] who composed a treatment protocol that was administered to 64 women consecutively admitted to the hospital for postpartum psychosis. The protocol had four treatment stages which were progressed through if symptom remission was not achieved at the preceding stage. A 98.4% remission rate was obtained using levels I–III. Level I of the protocol was the use of benzodiazepine monotherapy for 3 days to determine if optimizing sleep was sufficient to achieve remission. This was successful in 6.3% ($n = 4$) of the women. Step II involved augmenting the benzodiazepine with an antipsychotic, most commonly haloperidol or olanzapine. An additional 18.8% ($n = 12$) of the women achieved remission within 3 weeks of this stage. Adjunctive lithium was added to the treatment regime in stage III, and the dose was titrated to achieve a serum level of 0.8–1.2 mmol/L. An additional 75% of the women achieved remission in this stage. Stage IV was ECT, but this was not used in any of the women. Following the acute treatment, women were advised to remain on maintenance therapy for 9 months except for the women who remitted in stage I as they were tapered off the benzodiazepine after remission. None of the patients who remitted in stage I relapsed in the following 9 months. Fifty percent of the women who remitted in stage II and were maintained on an antipsychotic medication relapsed over the 9 months. For women who remitted in stage III, the benzodiazepine and antipsychotic were discontinued, and the women had maintenance treatment with lithium (serum lithium level 0.6–0.8 mmol/L). The relapse rate at 9 months in this group was 12.8%. The overall rate of remission at 9 months was 79.7% among the 64 women. An increasing body of literature suggests that sleep disruption may be a very important factor in both the development and prevention of postpartum psychosis [69, 70].

14.9 Conclusions

Pharmacological management of perinatal BD remains a highly complex area where the risks of the maternal illness must be estimated and weighed against the risks associated with mood stabilizing medications (Table 14.1). This balancing of risks must be performed on a case-by-case basis for each woman, but information pertaining to the risks associated with both the illness and the medications are lacking. Untreated maternal BD often leaves women at risk of significant morbidity,

Table 14.1 Expert recommendations for the management of perinatal bipolar disorder based on scientific and clinical experience

Perinatal period
1. Treatment decisions in the management of perinatal bipolar disorder should be individualized
2. Perinatal recurrences of bipolar disorder are usually characterized by depressive or mixed symptoms
3. Treatment decisions should take into consideration the past illness course (especially during the perinatal period), current symptoms, co-morbid psychiatric disorders, family psychiatric history and history of treatment response
4. Management of co-morbid psychiatric disorders and medical co-morbidities (e.g. obesity, smoking and substance abuse) is important in minimizing risks to both the mother and her baby
5. Use of mood stabilizing medications should be limited to monotherapy where possible
6. Valproate should not be prescribed to women during the childbearing years
Preconception
1. Preconception counselling should be an integral part of the plan to manage bipolar disorder during and after pregnancy
2. Women who have been clinically stable for at least 6 months and have had a mild illness course may be appropriate for tapering or discontinuing medications during pregnancy or in the preconception period
Pregnancy
1. Both mood stabilizing medications and untreated bipolar disorder can pose significant risks to the mother and foetus during pregnancy
2. Both the mother and foetus should be closely monitored during pregnancy
3. Lamotrigine may have the best pregnancy safety profile among mood stabilizing medications, but it lacks efficacy in managing hypomanic and manic episodes
4. Haloperidol is a preferred medication for management of mania during pregnancy
5. Careful balancing of risks and benefits is necessary when considering the use of lithium in pregnancy
6. Antidepressants should be given scrutiny in pregnancy as they have associated foetal risks and may precipitate mood instability, especially if mood stabilizers are discontinued
7. Valproate should be avoided during pregnancy because of its high teratogenic risk
Postpartum
1. Women with bipolar disorder require very close monitoring in the postpartum given the high rates of illness relapse during this time
2. Women who remain medication-free during pregnancy may benefit from the initiation of prophylactic mood stabilizing medications in the immediate postpartum

worsened obstetrical care and impaired capacity for childcare. Yet, many of the medications commonly used to manage BD, particularly some of the antiepileptic agents, are associated with significant risks to foetal development.

There are numerous aspects of perinatal BD pharmacology which require further study. To date no RCTs have been completed in this population. However, conducting RCTs in this population would likely be unfeasible given ethical concerns. Studies in the acute treatment of BD both during pregnancy and the postpartum are needed. Currently, evidence on the effectiveness of various mood stabilizing medications must be extrapolated from studies in non-perinatal populations, many of

which specifically excluded pregnant and postpartum women. Existing perinatal literature is heavily focused on BD I as there has only been a single study with exclusive focus on the management of perinatal BD II [71]. It is not yet known if there are significant pathophysiological differences between BD in the perinatal period versus BD in other periods of a woman's life. Should significant differences exist, this could suggest that a different approach to treatment would be indicated. Another emerging issue is a lack of pregnancy safety data for many of the newer antipsychotic medications being used to treat BD. This lack of data makes it very difficult for clinicians to discuss the risks of treatment with pregnant women which is vital in allowing them to make informed treatment decisions.

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Schizophrenia and Related Psychoses

15

Selma Bozkurt Zincir

15.1 Introduction

Schizophrenia is a severe psychiatric disorder which occurs in young age and affects the perception, thinking, feeling, psychomotor activity, behavior, and cognitive functions of the patient. Schizophrenia leads to dysfunction in the areas such as learning, self-care, working, social relationships, and daily life skills and might result in lots of problems in work and social life [1]. Although prevalence of schizophrenia in general population is less than the anxiety and depressive disorders, because the onset of the schizophrenia is obviously in reproductive ages, psychotic symptoms can be seen during the perinatal period [2].

15.2 Schizophrenia and Fertility

Women with the diagnosis of schizophrenia have lower fertility rates as compared to the general population. According to the findings of a society-based retrospective study conducted in Canada between 2002 and 2011, in every 1000 pregnancies, there are three mothers with schizophrenia [3]. Howard [4] suggests that schizophrenia is the most common psychiatric disorder which affects the reproducibility.

There are some underlying probable causes, for example, schizophrenia affects negatively keeping healthy social relationships, low marriage rates, sexual dysfunction due to illness or psychotropic medications, and suppression of ovulation due to hyperprolactinemia [5]. Nowadays there are some practices supporting deinstitutionalization of patients with severe psychiatric disorders from closed clinical settings, and they are supported to be in active daily social life. Having lower hyperprolactinemia rates with atypical antipsychotics increases the opportunity of

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these women being pregnant. Thus, according to the findings of a study conducted in the USA between 2000 and 2007, it was reported that antipsychotic drug usage was three in every 1000 pregnant women which increased up to eight in every 1000 pregnancies [6].

15.3 Clinical Features and Course of Schizophrenia During the Perinatal Period

There is not any proof that the risk of having schizophrenia in pregnancy is either increased or decreased [7]. Studies about clinical features and prognosis of schizophrenia in pregnancy are insufficient; thus it does not show whether it is a positive or negative effect. It has been reported that more than half of the patients with schizophrenia who shows active symptoms does not visit psychiatrists [4]. Retrospective studies highlighted that women with diagnosis of schizophrenia have exacerbation of symptoms rather than psychotic symptoms which appear for the first time [8]. Cessation of existing treatment or attempt to replace a currently effective drug in this period, by the concern of negative effect on the pregnancy, increases exacerbation risk even more [9]. Result of the reviews done about this subject is that women patients with schizophrenia whom antipsychotics are stopped have a recurrence rate of 50%, whereas for continued medical therapy, this rate was found to be about 15%. In other words, patients who stopped their antipsychotic drug treatment have two- to threefold increased possible recurrence risk compared to continuation of treatment and in sudden drug withdrawals have increased risk of recurrence compared to gradual withdrawals [10].

A meta-analysis concluded that psychotic relapse ratio of schizophrenic patients in pregnancy is 6.9%, as for postpartum 37.5%, and relapsing risk is higher at postpartum period than pregnancy [11]. According to observational studies, for more than half of the patients, psychiatric exacerbation is seen, and risk of psychotic recurrence increases approximately up to sevenfold in the first year especially in the first 3 months [4, 11]. Patients whose inpatient treatment history is more than 3 months and active symptoms are within 6 months before pregnancy have higher risk of psychotic relapse [12]. Of women diagnosed with schizophrenia, 8% have treatment in an inpatient clinic during pregnancy [4, 13].

15.4 Risks of Untreated Maternal Schizophrenia

It is reported that more than half of the patients with schizophrenia do not go to psychiatry follow-ups during their pregnancy despite the existence of active psychotic symptoms [4]. Studies about the effect of schizophrenia on pregnancy and developing fetus are increasing. While some coherent results are obtained in some studies, significant procedural differences between studies constitute an obstacle in accessing more clear information. The effects of schizophrenia on pregnancy and

fetus may be direct, but there are also indirect effects with various factors such as pregnancy planning, prenatal care, nutrition, and alcohol and substance use. The risk is further increased in patients without treatment [11, 14, 15].

It has been reported that vitamin intake during pregnancy is lower and antenatal care level is lower [11]. In a community-based study, preterm birth and low birth weight ratios are reported to be about two times higher than those who receive adequate care in schizophrenic mothers who do not receive adequate medical care during pregnancy. Women with schizophrenia are at risk for stillbirth, premature birth, low birth weight infants, and sudden infant deaths when pregnant [16–19].

While it is not clear enough in studies that the contribution of indirect factors and the adverse effects of which are directly related to the disorder itself, some authors suggest that the effect of maternal factors such as preterm birth, low birth weight, maternal age, parity, education level, and smoking on risk of stillbirth in schizophrenia is high even if they participate in the account, thus suggesting that risk increases cannot be explained only by maternal factors [18, 20, 21].

However, most recent studies have reported that women with schizophrenia have an increased risk of complications such as preeclampsia, thromboembolism, low birth weight infant, placental insufficiency, gestational diabetes, and premature birth during pregnancy [3, 22]. Hoirisch-Claupach and colleagues [22] noted that patients with severe mental impairment such as schizophrenia may have a low-activity tissue plasminogen activator and a procoagulant phenotype, which may contribute to placental failure. The risk of developing congenital cardiovascular anomalies in infants of women with schizophrenia is increased [17]. There is also an increased risk of obstetric complications involving placental abnormalities and prenatal bleeds in the pregnancy of schizophrenic patients [17, 22]. Nosarti et al. [23] reported that women who had recently published schizophrenia had a 1.6-fold increased risk of premature birth [23]. Studies show that LBW (low birth weight) increases 1.2- to 2.3-fold in infants of mothers with schizophrenia [17–19, 22]. About 1.1% of schizophrenic mothers lose their babies in the first year, and the risk is 2–2.5 times more likely than controls [16, 18–20, 24]. Sudden infant death syndrome risk is reported to be 0.5% and is about five times higher [16, 22, 25]. Both clinical conditions seem to be related to schizophrenia regardless of demographic factors [16, 18, 19].

15.5 Psychopharmacologic Treatment of Schizophrenia in the Perinatal Period

15.5.1 Pregnancy

Due to several reasons, pregnancy of women with schizophrenia is accepted as a relative risk. Pregnancy can trigger psychophysiological decompensation for women diagnosed with schizophrenia. Certain risk factors for pregnancy in schizophrenia are realization of pregnancy with delay, having reduced prenatal care and routine follow-up visit, excessive smoking, and inability to notice and understand

the start of labor. There may be patients reporting hallucinations leading to deny pregnancy or to refuse prenatal ultrasound examination. In these cases, risks of having unaided labor and failure of mother-baby bond are high. For these patients, there can be either obstetric or psychiatric complications [19, 20].

Routine treatment suggestions of pregnancy period are not found, and with regard to developing baby's safety, it is hard to have an absolute conclusion about these treatments. Selection of antipsychotic for treatment of pregnant women with schizophrenia, especially when it comes to application of new agents, is a complicated process [9, 26, 27]. Effects of treatment on the fetus should be considered besides its effects on the patient. Every pregnant woman should be evaluated by her own special condition [9]. Regarding the ethical issues, none of the studies about drugs that have been used does not meet gold standards as randomized, placebo-controlled, double-blind, crossover studies. Very few studies are conducted by controlling patient's age, past pregnancy losses, antipsychotic dosages, timing of administration, and usage of multiple drugs or illegal agent [9, 27].

Single antipsychotic drug use and minimum effective dose should be preferred for pregnant women as possible; treatment should be given in divided doses. Later in pregnancy, as a result of weight gain, metabolism, excretion of drug, and muscle/fat ratio changes, increased doses might be needed [9]. Still, maintenance of current stabilization in terms of mental aspect is the main subject for consideration, and sometimes more than one agent can be needed. Risk/benefit argument for antipsychotic drug treatment is designed by the woman's treatment history. Selection of the most appropriate treatment course rather than right or wrong choice should be the main target. Replacement of currently effective treatment with a safer drug is not recommended; however, if there is a pre-existing response to a safer drug in patient's history, a modification may be considered [9, 12]. In addition, while considering secondary conditions [complications] to drug use, rather than medication, negative results of the disease [low birth weight, early labor, occurrence of problems in the long terms, a worse manifestation in lactation period, etc.] that might affect the course of pregnancy should be kept in mind [12]. While detecting if a drug is whether teratogen or not, appeared defect should have a distinctive pattern [like extremity problems appear with thalidomide] or should appear more than 3% which is the general ratio of defects in newborns [9].

Considering the findings of Einarson's several studies in recent years, first-generation antipsychotics (FGAs) are accepted as relatively safe [28]. It has been reported that women taking piperidyl piperazine [fluphenazine, trifluoperazine, and perphenazine], phenothiazine [chlorpromazine, thioridazine, and promethazine], butyrophenone [haloperidol], tioksanten [flupentixol], dibenzoksapin, or diphenylbutylpiperidine group of typical antipsychotics do not have an increase in teratogenicity [28]. By now, there are no certain results that are concluded for second-generation antipsychotic (SGA) use in women at reproductive ages or in pregnant women. In addition, generally SGAs have better safety profiles when compared to FGAs [29].

Poo and Agius' report published in 2015 reports the last suggestions and updates for pregnancy and breastfeeding period of NICE treatment guide [30, 31]. In this specific period, while considering pharmacological treatment for minimizing the risks for the mother and baby, encouragement of psychological trials in the first place as possible shows the broadest perspective. It is known that SGAs are related to metabolic complications like weight gain and DM II. But the relationship between antipsychotics and undesired defects and pregnancy is not shown clearly [30].

A currently published article by Jayashri et al. in 2015 reported that there are not any data that shows most commonly prescribed SGAs such as olanzapine, quetiapine, and risperidone increase congenital disorder and fetal malformation [32]. In a population-based comparative cohort study, it is stated that there aren't any differences in terms of major malformations, but low birth weight and therapeutic abortion are more common in people taking SGAs such as olanzapine, quetiapine, risperidone and clozapine compared to those who are not [33]. In a recent wide population-based study, small babies are increased depending on the age of pregnancy; in addition, when mother-related factors are considered, this difference showed not to be statistically meaningful [34]. In a current review, Kulkarni et al. [35] reported that there is no increased rate of teratogenicity with the usage of SGAs such as clozapine, olanzapine, quetiapine, and risperidone during pregnancy. Specific malformation of a fetal organ or extremity is not reported with the usage of those antipsychotics [35]. Data about other new-generation antipsychotics (e.g., aripiprazole, ziprasidone, and paliperidone) are based on few case reports and do not show any extraordinary increase of specific malformations [9, 36].

A systematic review published in 2010 about the usage of SGAs showed effects on metabolic complications in pregnancy (Gestational DM, obesity); birth defects and low-weight for gestation age (LGA) risk are increased [36]. It is difficult to distinguish if metabolic complications appeared are related to SGAs from pregnancy or not. Actually, for women who suffer from metabolic diseases (either with psychiatric disorder or not), risk of the obstetric complications is at high level. According to the results of Boden et al.'s study [34], gestational DM is reported more than two times in women who use antipsychotics (4.2%) than those who are not using (1.5%). According to a few numbers of wide-scale studies, clozapine was related especially to major fetal malformations. But in these studies, the relation of causality is not certain [36].

According to a study based on a wide population, women with severe psychiatric disorders such as schizophrenia and bipolar disorder have increased risk of pregnancy-related complications compared to the general population [17]. Hence, it is difficult to specify the origins of obstetric complications, and neonatal results are from either diseases, drugs, and interfering factors or incidentally. Also, it is difficult to specify the causative agents because these patients are frequently under the effect of polypharmacological treatment [17].

Robakis and Williams [37] emphasized safety rather than effectiveness in their current review while they argue between pediatricians and obstetricians on the algorithm that guides the choice of SGA on treating pregnant women.

15.5.2 Postpartum Period

Postpartum period is one of the most dangerous periods for exacerbation of psychiatric disorders and rehospitalization in women's life. For this reason, to prevent a potential psychotic exacerbation during pregnancy and after birth, exceptional attention is necessary. It might be necessary to use antipsychotic agents in exacerbation of disease just after the birth (or in the third trimester) or for the women with schizophrenia [38].

A successful antipsychotic treatment at the perinatal period is a result of good multidisciplinary cooperation between obstetricians, general practitioners, and psychiatrists [9, 12]. Risk of acute psychotic exacerbation at schizophrenia is mostly seen at the first 3 months after birth [39]. Physiologically, progesterone and estrogen levels are lowest at the first few days of postpartum period. Loss of antidopaminergic activity of estrogen may increase the risk of decompensation for psychosis [40]. Clinical manifestation of the women with schizophrenia, exacerbation related to leaving the medical treatment or stress factors at the postpartum period, has a risk of harm to the baby [41, 42].

As impairment of a mother's psychological situation may result in breakdown of healthy mother-baby bonding, it may also affect negatively the baby's cognitive and behavioral development. Breastfeeding must be encouraged not only for safe mother-baby relation but also for decreasing the risk of infection and death ratios [43]. Breastfeeding is described as the best feeding source for the first 6 months of the baby [43]. Besides as many women desire to breastfeed their babies, they are unwilling to take psychiatric disorders' treatment during postpartum period [41, 44]. For this reason there is a need of safety data about antipsychotics in order to decrease unintended exposition of the baby and preserve the mother's psychiatric health ideally [45, 46].

During the perinatal period, psychotic exacerbation or onset of schizophrenia may increase the risk of mortality and morbidity so it is important to treat properly and with great attention. Besides, because babies of untreated mothers are less susceptible to their babies, it is reported that these children are at increased risk of psychical and emotional neglect and abuse [47, 48]. Choosing an antipsychotic for the treatment of a woman with schizophrenia at perinatal period requires considering about many issues with regard to the patient, and general activity profile of the antipsychotics is the best approach for personalization of the treatment. In general, if the patient had used a specific type of antipsychotic agent before and benefit from it, that antipsychotic agent is prior to choose [44].

All the data up to date show that in breastfeeding women with schizophrenia and related psychotic disorders, it is very difficult to decide risk/benefit profiles of the antipsychotics for the babies. Although there is limited data, current information shows that it is not contraindicated to use antipsychotic drugs while breastfeeding [43].

Studies that investigate the usage of FGAs during the breastfeeding period and milk/plasma ratio are determined in a consistent way as small, and there are no reported toxic or adverse effects [43]. According to the research results and case

reports it is possible to reach outcomes of; most of the undesirable outcomes are not relevant to SGA, detected at acceptable and safe levels on breastfed babies and mild, temporary side effects (such as sedation) are seen. For this reason, the risk of leaving the mother with psychotic disorder untreated is higher than transmission of low amount of drug to the baby [41].

If the woman with schizophrenia on postpartum period wants to breastfeed, single SGA should be given at low dose. According to current literature, drug of choice for breastfeeding women should be olanzapine. Because of the very low RID values, quetiapine may be given as first- or second-line treatment, but there is very limited data [49]. Risperidone has relatively high RID value than these two drugs; it is suggested as the second-line therapy while breastfeeding. Clozapine usage must be avoided as possible in the breastfeeding period. For reliable suggestion for usage of aripiprazole, amisulpride, and ziprasidone, there is a requirement for more data.

In the breastfeeding period, chlorpromazine, haloperidol, and zuclopenthixol must be given at minimum possible doses and only with continuous monitoring [45]. In the available data about SGAs, they are used mostly between the first week and sixth month after birth; and maternal dose range is 2.5–20 mg/g [7.52 mg/day] for olanzapine, 25–400 mg/day [med, 183.92 mg/day] for quetiapine, 1–6 mg/day [med, 3.18 mg/day] for risperidone, 10–18 mg/day [med, 14.5 mg/day] for aripiprazole, 40–160 mg/day for ziprasidone, 250–400 mg for amisulpride, and 100 mg/day for clozapine [38]. It is early to talk about long-term effects of antipsychotics regarding to these studies, which are conducted less than 18 months [41]. The longest follow-up study related to the usage of AP agents at postpartum period belongs to Mendhekar (2007) [50]. In this study, children of women who used clozapine at the period of pregnancy and breastfeeding period are followed up for 5 years and dwell on the latency of verbal skills [50]. Measuring antipsychotic levels on baby's plasma or breast milk is a useful but very difficult way. As it is more practical, parents should be instructed about the negative effects of antipsychotics (respiratory problems, chill, irritability, hypoglycemia, feeding difficulties, sleeping problems, rigidity, jaundice) and should be evaluated by a pediatrician frequently [2].

15.6 Conclusion

The pharmacological management of schizophrenia in women of reproductive age is highly complex and requires a holistic approach in order to maximize both the maternal and child's physical and mental well-being [30]. NICE CG192 presents the current evidence on atypical antipsychotics for schizophrenia in pregnancy; and good management requires a solid understanding of the illnesses themselves and the pharmacodynamics of the medications used. Although firm conclusions cannot be drawn at this stage, current studies have improved our understanding on the pharmacology and risk: benefit profile of these drugs, with each antipsychotic having varying efficacy and side effects. Each treatment option should therefore be thoroughly discussed, and the decision should be based on balancing the benefits and risks, with considerations for patient

preference and other patient factors. There is also a strong emphasis on continuous monitoring and modulation of drugs in order to ascertain the best possible outcome for patients. There is a need of well-designed prospective studies for the proper evaluation of development for the children of the women who used antipsychotic drugs at the perinatal period. In these studies, besides maternal psychiatric disorders, alcohol use, drug use, and exposure to drugs should be reported with certain measurements (Table 15.1).

Table 15.1 Expert recommendations based on scientific evidence and clinical experience

1. Considering the potential of pregnancy as much as possible, the best pharmacological treatment approach should be planned from the beginning of pregnancy. Therapeutic cooperation should be well established, and nondrug treatments should be tailored
2. Close cooperation should be ensured among all disciplines involved in perinatal care, such as psychiatry, psychology, gynecology, pediatrics, midwifery, social worker, and maternal-infant health nursing
3. In addition to remaining untreated during the perinatal period, it should be ensured that written consent is obtained after the patient and his/her relatives have been informed in detail of the current available data on the benefits and risks of the treatment to be performed
4. Baseline measurements of basic biological parameters compatible with mental disorders and treatment should be obtained. Measure prolactin levels in patients taking prolactin-raising antipsychotics; if raised, consider prolactin-sparing antipsychotic. Continue antipsychotic if she is likely to relapse without medication. Do not offer depot antipsychotics in women who are planning a pregnancy, pregnant, or considering breastfeeding, unless she is responding well to depot and has previous history of nonadherence to oral medication
5. Monotherapy should be targeted as much as possible. Antipsychotic treatment should be given in a minimal effective dose. However, it should be avoided ineffective low doses. It should not be forgotten that the fetus will be exposed to both congenital and untreated outcomes with incomplete treatment
6. During pregnancy, fetal development, obstetric physiology, and changes in maternal mental status should be adequately monitored. Ideally, a treatment team specializing in high-risk scenarios should undertake obstetric care. Similarly, close monitoring of fetal development (preferably weekly at 28, 32, 34, and 36 weeks and weeks after) is crucial for increased risks, such as low and high birth weight
7. At the 12th week of pregnancy, an ultrasound examination of the nuchal translucency of the fetus should be performed followed by a high-resolution morphology scan at 20 weeks
8. Because of the potential for increased risk for metabolic syndrome and gestational diabetes with secondgeneration antipsychotics, glucose tolerance test should be performed from week 16 to week 28 and the glucose uptake test from week 28 to the birth.
9. At birth, close observation and careful morphological examination should be performed in terms of withdrawal symptoms, toxicity, extrapyramidal symptoms, sleepiness, or other adverse effects that may occur in the newborn
10. Early warning signs for the relocation of existing psychiatric disorder and those to be performed for necessary care should be prescribed in case of a relapse
11. Discussion of the risks and benefits of using certain antipsychotic medications during breastfeeding with the patients and their relatives in the prenatal period and, accordingly, advice and priorities should be given on breastfeeding. Pharmacological suppression of lactation should be avoided. Encourage breastfeeding unless patients are taking clozapine. The level of antipsychotic medication in breast milk depends on the drug

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Obsessive-Compulsive Disorder

16

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16.1 Introduction

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder frequently emerging among women in the reproductive years [1–3]. Its major characteristics include marked anxiety in the patients and disturbances in academic, occupational, and social functions [4–6]. In addition, OCD may lead to a considerable reduction in the quality of life, often to the same extent as schizophrenia [4].

Epidemiological studies have suggested that OCD represents the fourth most frequent psychiatric diagnosis following substance use disorders, mood disorders, and phobias [2]. In recent years, many studies have examined whether reproductive events in women such as pregnancy and the postpartum period may be associated with OCD. Some authors have noted that female OCD patients reported pregnancy and childbirth to be precipitating events for the onset of OCD [7, 8]. While the prevalence rate of this disorder was reported as 1.8–3.3% of women in the general population [2, 9], it was observed in 0.2–5.2% of pregnant women [10–17] and 0.7–9.0% of postpartum women [11, 18–21]. A recent meta-analysis has suggested that pregnant and postpartum women were an increased risk of 2.07- and 2.43-fold, respectively, to experience OCD compared to the general population [22]. In addition, the perinatal period may affect the course of OCD in women [23–25]. On the other hand, inarguably, the newborn requires maternal attention, which emphasizes the importance of the treatment of OCD during this period.

Pharmacotherapy and psychotherapy are two main treatment regimens in OCD. Cognitive behavioral therapy (CBT) is the most effective evidence-based psychotherapy for OCD [26]. Although it has been suggested that this method is as effective as pharmacotherapy [27, 28], this chapter will not discuss CBT as a treatment method as it is not relevant to the theme of the book.

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16.2 Risks of Untreated OCD

The emotional state of the mother during the perinatal period can have both short-term and long-term effects on her child [29]. Anxiety is one of the core symptoms of OCD. Studies have suggested that maternal antenatal and postnatal anxiety is associated with an increased risk of preterm birth and low birth weight, disturbances in sleep and feeding of the infant, lower maternal bonding, decreased interactions between the mother and the infant, and increased risks of cognitive, emotional, and behavioral problems in the child stage [30–35]. OCD may have similar negative effects on the fetus or infants; however, studies examining this hypothesis are very limited. Some authors have reported that birth weight and gestational age were lower in newborns exposed to maternal OCD compared to babies who were not exposed [36]. However, these findings were not confirmed by further studies [37, 38]. Long-term effects of perinatal maternal OCD on the infants remain unknown. Results of a study with small sample size suggested that maternal OCD, particularly in those patients with higher maternal anxiety levels, may affect brain development of the fetus via increased neuroinflammation [39]. In addition, it was recently suggested that maternal postpartum OCD was associated with lower sensitivity during interactions with infants [40].

16.3 Pharmacological Treatment

The effectiveness of pharmacological treatments including serotonergic antidepressants and their augmentation with antipsychotics is well documented. Despite noteworthy advances in non-perinatal patients, pharmacological treatment and treatment guidelines for psychiatric disorders in perinatal patients have been largely neglected. Major issues in determining treatment regimen for OCD in women during pregnancy and lactation are possible adverse events in the fetus and breastfed infants due to psychotropic medications. In contrast, due to potential negative effects of maternal OCD and secondary anxiety or depression on fetuses or infants, the risk of not treating this disorder during the perinatal period exists. However, to date, no study examining whether pharmacotherapy is useful in decreasing possible negative effects of untreated OCD has been published in the literature. Therefore, recommending the safest and most effective pharmacological approach for the mother and her baby in this chapter is challenging.

16.3.1 General Considerations

The decision regarding the pharmacological treatment regimen should be based on several factors such as the risk of untreated maternal psychiatric illness, the known or unknown potential effects of psychotropic medications, benefits of pharmacological treatment, and alternative treatments to medication [41]. A careful psychiatric assessment should include individual and family history of psychiatric disorders,

side effects or therapeutic effects of medications used previously, severity of the disorder, comorbid conditions, duration of remissions both on and off medications, time to relapse after previous discontinuation, time to recover on reintroduction of medication, frequency of and triggers for relapse, and degree of impairment in occupational, family, and social areas secondary to the disorder [42, 43].

There are five main clinical rules in the pharmacological treatment of OCD during pregnancy and the lactation period: First, the treatment should be individualized. Second, the benefits and risks of untreated and treated OCD for the mother, her baby, and her family including other children should be discussed with the mother and her relatives. These discussions and the patient's choice should be documented. Third, all steps of the treatment should be administered in agreement with the patient and her relatives. Fourth, psychotropics with an evidence base with regard to both efficacy and safety in pregnant or lactating women should be chosen. Fifth, the clinical status and response to the treatment of the patients should be closely monitored [44]. Other general recommendations are as follows [42, 45]: (1) The lowest therapeutic (but not sub-theraputic) doses should be chosen to minimize fetus/infant exposure. (2) Using a drug of known efficacy in the patient may be preferable to using one with unknown efficacy. (3) If a decision is taken to discontinue medication, this should be carried out as slowly as possible. (4) Although some patients require the use of combined antipsychotics, monotherapy is essential. If combination is inevitable, the second medication should be used as briefly as possible. (5) Older medications are preferred to newer medications, if there are inadequate data on infant safety.

Another issue in clinical practice is the decision on which patients actually need to be treated pharmacologically. There is no consensus on clinical indications for initiating pharmacological treatment in perinatal women with OCD, because there are no comparative studies on the influence of OCD untreated or treated by antidepressants in pregnant or lactating women with similar clinical features. However, pharmacological options may be considered in patients with severe depression and anxiety symptoms, a high risk of suicidal attempts, considerable feeding and sleep disturbances secondary to OCD, or OCD that is unresponsive to cognitive behavioral therapy [44].

16.3.2 Treatment of Active Symptoms

16.3.2.1 First-Line Treatment

To date, clinical guidelines for the treatment of OCD in pregnant or lactating women have not been published in the literature. Overall, it is assumed that these drugs are also effective in the perinatal period despite the lack of placebo-controlled studies [44]. Moreover, none of the specific antiobsessional drugs are contraindicated for use during pregnancy and the lactation period.

Selective serotonin reuptake inhibitors (SSRIs) and clomipramine are first-line medications for OCD in the non-perinatal period [46]. Compared to SSRIs, clomipramine has greater or equivalent efficacy in OCD; however, its lower tolerability by

the patients led to a marked decrease in prescribing the drug [26, 47]. In addition, when the limited data on safety of clomipramine during pregnancy and results of several studies suggesting increased risk of cardiac malformations and severe perinatal complications are considered, this drug does not appear to be appropriate as first line in the treatment of pregnant women with OCD. Similarly, factors such as limited available data on its safety, higher risk for propensity to convulsions, and increased risk of arrhythmia restrict its choice during lactation [26, 48, 49]. The available scientific evidence on safety suggests that clomipramine should be cautiously preferred in pregnant and breastfeeding women with OCD who cannot tolerate or who have failed to respond to SSRIs [44, 47].

SSRIs are recommended as first-line pharmacological agents for OCD in the perinatal period based on a relatively large database regarding their safety on the fetus and breastfed infants [42]. Some authors reported that the most commonly prescribed SSRIs in non-perinatal inpatients are sertraline, citalopram, and paroxetine [50]. The current evidence does not support the superior efficacy or tolerability of specific SSRIs to each other in OCD [51]. The most important factors affecting the decision regarding which SSRI can be prescribed to perinatal patients with OCD are the available scientific data on safety of each SSRI during pregnancy and lactation as well as a history of their effectivity and tolerability in the mother in the past.

Despite some negative reports, sertraline and citalopram/escitalopram seem to be more favorable as pharmacological options during pregnancy based on their safety in the fetus [44, 52–56]. However, the advantages of sertraline compared to citalopram/escitalopram are that the treatment can be continued during breastfeeding due to a high safety index, and there is much stronger evidence on efficacy in OCD [53, 57]. There is limited data in the literature on the safety of fluvoxamine; therefore, this antidepressant is not recommended during pregnancy [53]. Despite the highest amount of data, clinicians have some concerns about the use of fluoxetine during pregnancy, because there is growing evidence suggesting increased risk of fetal defects and because the drug is released slowly in the body of the newborns [44, 53]. Similarly, it has been accepted that paroxetine is associated with an increased risk of congenital malformations, especially cardiac types [54, 58]. Owing to these features, fluoxetine and paroxetine are not appropriate for first-line treatments of OCD in pregnant women [44, 53, 56]. However, these antidepressants show low elevation of absolute risk of birth defects and may be used in patients with OCD who cannot tolerate or do not respond to sertraline, citalopram, or escitalopram [44, 54, 58].

There is a consensus in the literature on sertraline and paroxetine as first-line SSRIs during the lactation period because of adequate scientific data on their safety in breastfed infants. Citalopram/escitalopram and especially fluoxetine are less favorable. Citalopram/escitalopram does not accumulate, which is more advantageous compared to fluoxetine. Fluvoxamine should be used cautiously due to very limited data on its use during lactation [45, 59–61].

Several studies have suggested that venlafaxine may be efficient in the treatment of OCD [62, 63]. Its safety profile in pregnancy appears to be similar to SSRIs [41, 64–66]. Moreover, the fact that adverse events have been rarely reported in breastfed infants encourages the use of this antidepressant during the lactation period

[60]. On the other hand, limited available evidence of venlafaxine on efficacy in OCD and safety during pregnancy and breastfeeding are major disadvantages for its use. This paper recommends the use of venlafaxine prior to combined pharmacological options if pregnant or breastfeeding women with OCD do not respond to monotherapy with other antiobsessional antidepressants and have severe comorbid psychiatric disorders such as major depression, generalized anxiety disorder, and panic disorder.

16.3.2.2 Non-response to the First-Line Treatments

Approximately half of the patients with OCD who receive serotonergic antidepressant monotherapy at adequate doses and durations do not experience clinically significant improvement in symptoms [46]. Initially, accuracy of the current diagnosis, possible medical or psychiatric comorbidities, degree of response, and treatment compliance in the patients should be carefully reviewed by the psychiatrist [44, 51, 67]. There are several pharmacological approaches in unresponsive patients: switch between antidepressants, treatment with initial SSRI at a supratherapeutic dose, combining SSRI and clomipramine, and augmentation with antipsychotics [46, 51]. Due to the lack of randomized controlled studies, which option is safer and effective in pregnant or breastfeeding women is currently unknown [61].

Switch Between Antidepressants

Despite insufficient scientific evidence, switching from one SSRI to another in patients who do not respond is an acceptable pharmacological option that is performed commonly in clinical practice [51, 68]. Several studies have suggested that about 40% of the patients experience clinically significant reduction in OCD symptoms [51, 69]. Although there are no studies conducted in the perinatal period, clinical experience implies that the switching method may be effective in a considerable number of pregnant or postpartum women with OCD. When safety in the fetus and/or breastfed infants is considered, this strategy may be more favorable as the first step in perinatal women compared to other pharmacological strategies. Switching between sertraline and citalopram/escitalopram during pregnancy and between sertraline and paroxetine during breastfeeding may be appropriate [44, 61].

SSRI Treatment at Supratherapeutic Doses

High-dose treatment with SSRIs even at two- to threefold of the maximum therapeutic doses is another pharmacological strategy [51, 70–72]. However, data supporting the benefits of this strategy is limited in non-perinatal patients [51]. Additionally, potential effects of SSRIs at supratherapeutic doses on the fetus or breastfed infants are unknown. Some authors reported that high doses of SSRIs (e.g., more than 40 mg/day for fluoxetine, citalopram, and paroxetine), even within the therapeutic dose limits, are associated with 2.5- to 5-fold higher risk of preterm birth compared to lower daily doses [73–75]. As a result, this is not a good pharmacological option in unresponsive perinatal women with OCD. If administration of such high doses indeed becomes necessary, the pregnant patient and exposed infants must be followed closely by the mother and physicians [44].

Combination Between Clomipramine and SSRIs

Clinicians frequently use this combinatorial method in non-perinatal women with SSRI-resistant OCD. Nevertheless, this strategy does not seem to be feasible as the first or second line of pharmacotherapy in the pregnancy and lactation period due to the following reasons: (1) studies examining the efficacy of this combination in OCD are few, and their results are controversial [46, 76, 77], (2) there are no data on safety of the fetus and/or breastfed infants in the literature, and (3) this combination, especially between clomipramine and paroxetine or fluoxetine, is associated with a risk of clinically significant pharmacokinetic interactions that could lead to a dangerous buildup of clomipramine [51].

Augmentation with Antipsychotics

In the non-perinatal period, the most convincing evidence of treatment of SSRI-resistant OCD was with adjunctive antipsychotics [51]. This strategy is recommended in the treatment guidelines [46, 57]. It has been reported that adjunctive antipsychotics are prescribed in 30–40% of patients using SSRIs. The most commonly administered antipsychotics are risperidone, quetiapine, and olanzapine [50, 78]. Actually, there is no clear evidence suggesting the superiority of one antipsychotic drug over others, because comparative studies between different antipsychotic augmentations are very limited.

Risperidone is an antipsychotic with the most consistent successful results that are supported by meta-analyses [79–82]. Augmentation with haloperidol was found to be effective in at least two meta-analyses in spite of being used in only one placebo-controlled study [79, 81]. Randomized controlled studies [83–85] and one meta-analysis [82] indicated efficacy of augmentation with aripiprazole. Moreover, the Canadian clinical practice guideline [57] recommends the use of aripiprazole in addition to risperidone as the first-line adjunctive therapy. Despite at least one positive randomized controlled trial [47], four meta-analyses [79–82] have suggested that augmentation with olanzapine and quetiapine was not superior to placebo. Quetiapine has one positive meta-analysis based on changes from the baseline in total Yale-Brown Obsessive-Compulsive Scale [86]. Recently, Shoja Shafti and Kaviani [87] have suggested that treatment-resistant OCD patients may benefit more from the addition of quetiapine than aripiprazole. Additionally, quetiapine is also the single antipsychotic agent that has been studied perinatally. Misri and Milis [88] suggested that 78.6% of postpartum women with OCD were responders to augmentation with quetiapine.

This strategy may be theoretically effective in some perinatal patients. Nonetheless, there are no studies examining the safety of a combination of antidepressants and antipsychotics during pregnancy and lactation in the literature [44]. Antipsychotic augmentation is effective in approximately 30% of treatment-resistant non-perinatal patients, and it has potentially higher adverse effects on the fetus, the breastfed infant, or the mother [26, 44]. Consequently, this strategy should be preferred in case there is a clinical conviction that the augmentation has higher benefits compared to untreated OCD. After the decision to augment with antipsychotics is made, the drug should be used at as low doses as possible [44]. On the other hand, based on scientific evidences on effectivity in non-perinatal patients and

safety on the fetuses and breastfed infants, an augmentation with low-dose antipsychotics (e.g., 0.5–1 mg/day for risperidone, 2.5–5 mg/day for olanzapine, 100–200 mg/day for quetiapine) may be a more appropriate pharmacological option compared to high-dose SSRI administration and combination between SSRI and clomipramine at therapeutic doses.

Risperidone appears to be the most preferable antipsychotic during both pregnancy and lactation. This stems from the lack of clear evidence suggesting its association with increased risk of birth defects, reports of usage during breastfeeding being uneventful, and the existence of consistent studies and meta-analyses indicating its effectivity in OCD as an adjuvant [44, 61]. If the mother and/or the breastfed infant cannot tolerate this medication, or the patient does not respond to adjuvant risperidone, alternative antipsychotics including haloperidol, quetiapine, and olanzapine should be discussed for further augmentation. If the patient has severe anxiety and markedly decreased sleep and appetite, quetiapine and olanzapine may be more appropriate antipsychotics, respectively. Owing to limited data on safety during pregnancy and lactation, currently aripiprazole does not seem to be preferable during the perinatal period for treating OCD.

16.3.3 Prophylactic Treatment

It is well known that OCD has a chronic course in which recurrence and remission in the symptoms are observed. Studies have suggested a high symptomatic relapse after discontinuation of antiobsessional treatment [47]. On the other hand, many women with OCD at remission apply to psychiatrists when planning for their pregnancy or determining a management strategy during pregnancy or postpartum period. Indeed, there are no guidelines in the literature regarding pharmacological prophylaxis of OCD symptoms during pregnancy or the lactation period in patients who are symptomatically in remission. An exceptional consensus among perinatal psychiatrists is that the pharmacological management should be individualized after a careful clinical evaluation including current mental status and OCD characteristics, treatment response, and symptomatic relapse in the past.

This paper recommends treatment approach for active symptoms mentioned above if the patient has moderate or severe symptoms. In this part of the chapter, the recommendations for prophylaxis will be presented based on following clinical scenarios:

1. *Current mental status*: Symptomatically in remission (no longer meets syndromal criteria for the disorder and has no more than minimal symptoms) [89].
2. *Current mental status*: Symptomatically non-remitted but mild clinical severity of the symptoms.

(a) *History of the disorder*: Severe OCD symptoms and functional impairment, low response rate and late response to pharmacotherapy, sudden symptomatic relapse following discontinuation of pharmacotherapy, and comorbidity with depression and/or anxiety disorders.

(b) *History of the disorder*: Mild to moderate OCD symptoms and functional impairment, high response rate and immediate response to pharmacotherapy, no symptomatic relapse or relapse for a long time after the discontinuation of pharmacotherapy, and no comorbidity with depression and/or anxiety disorders.

If the decision is to continue with medication, previously used psychotropics may not be discontinued since absolute risks are low even with agents that are potentially associated with increased risk of birth defects or lack a clear contraindication regarding their use during breastfeeding. However, a switch from other antiobsessional antidepressants to sertraline or citalopram/escitalopram in pregnancy and sertraline or paroxetine in the lactation period may be more suitable with respect to safety of the fetus if the patient history indicates that these drugs are effective and tolerated by the patients. Additionally, prophylaxis with an SSRI is preferred to polypharmacy due to possible higher risks in the fetus and breastfed infants exposed to multiple drugs.

16.3.3.1 Pre-conceptional Phase

A reasonable period in psychiatric patients (at least 6 months) of clinical stability (mild or no symptoms) before attempting to conceive is recommended [43]. If the patient meets this recommendation, two main strategies should be discussed with the patient and her relatives before conception: (1) the medication is gradually discontinued after the last interview, and (2) the medication is continued until conception and then discontinued as soon as the pregnancy is detected. The duration from decision to conceive to an actual pregnancy cannot be predicted. Therefore, the major disadvantage of the first option is symptomatic relapse until conception. In the second option, this risk may be prevented; however, the fetus is exposed to the medication in the second to fourth weeks of pregnancy. Table 16.1 summarizes the recommendations by this paper on the basis of different scenarios mentioned above and management strategies.

16.3.3.2 Pregnancy

Retrospective studies have suggested that the severity of OCD symptoms worsened in 8–46%, improved in 8–28%, and remained unchanged in 31–69% of pregnant women [16, 23–25, 90–92]. A prospective study by House et al. [38] reported that there was no significant change in the severity of preexisting OCD symptoms. Worsening of the symptoms during this period seems to be associated with a history of individual major depression, presence of major depression and an anxiety disorder at the onset of pregnancy, contamination, symmetry/exactness obsessions, and cleaning/washing and ordering/arranging compulsions in the patient [92]. These findings should be kept in mind prior to making any decision regarding management of the treatment regimen during pregnancy.

If a pregnant patient has clinical features of scenario 1b, antiobsessional drug may not be needed until the recurrence of symptoms. In scenario 1a, either prophylaxis with an SSRI especially sertraline or citalopram/escitalopram at the lowest therapeutic dose or no medication with frequent clinical controls until the initiation of

Table 16.1 Management strategies recommended by this paper for prophylaxis of OCD symptoms based on clinical scenarios (please see the text for details) in the pre-conceptional phase, pregnancy, and the postpartum period

Clinical scenario	Management strategy
Pre-conceptional phase	
1a	Continue the medication until conception
1b	Gradually discontinue the medication
2a	Continue the medication until conception
2b	Continue the medication until conception
Pregnancy	
1a	Consider the following options: 1. Clinical monitoring without medication until the relapse of symptoms 2. Clinical monitoring without medication for the first 12 weeks of pregnancy, after that prophylaxis with a SSRI 3. Prophylaxis with an SSRI at the lowest therapeutic dose
1b	Clinical monitoring without medication until symptomatic relapse
2a	Prophylaxis with an SSRI at the lowest therapeutic dose
2b	Clinical monitoring without medication until symptomatic exacerbation
Postpartum period	
1a	Discuss the prophylactic treatment with the patient and her family
1b	Clinical monitoring without medication until symptomatic relapse
2a	Prophylaxis with an SSRI at the lowest therapeutic dose
2b	Clinical monitoring without medication until symptomatic exacerbation

OCD obsessive-compulsive disorder, *SSRI* selective serotonin reuptake inhibitor

symptomatic relapse and until the end of the first trimester of pregnancy may be discussed. It is unknown whether pharmacological treatment in pregnant women with OCD with mild severity of symptoms is superior to untreated OCD with respect to neonatal outcomes. In addition, as mentioned above, at least half of the patients do not experience any exacerbation in OCD symptoms during pregnancy. Therefore, in scenario 2b, the patient may not require any prophylactic treatment. For patients that match scenario 2a based on the history of the disorder, prophylaxis with an SSRI at the lowest therapeutic dose appears to be more appropriate (Table 16.1).

16.3.3.3 Postpartum Period

It has been reported that obsessive-compulsive symptoms remain unchanged in approximately half of the patients during the postpartum period [23–25, 90, 91]. There are two prospective studies suggesting significant reduction [93] or no significant change [38] in the severity of symptoms.

Postpartum women in scenario 1b and 2b may not receive any prophylactic treatment. In contrast, for patients in scenario 2a, this paper recommends clinical monitoring with an SSRI, especially sertraline or paroxetine, at the lowest therapeutic dose. Prophylactic treatment should be discussed with the patient and her relatives if the patient is considered to be in scenario 1a. If no prophylaxis is decided, it is recommended that the medication is administered as soon as the symptoms are initiated (Table 16.2).

Table 16.2 Expert recommendations based on scientific evidence and clinical experience

There are risks of untreated OCD as well as the medications on the fetus or infants
Treatment decision should be based on a careful psychiatric assessment, including individual history of OCD and current mental status
The treatment should be individualized
Both the patients and the exposed fetus or infant should be closely monitored
Monotherapy and lowest therapeutic doses are preferred to combinations of medication and high daily doses
The first-line agents recommended for treating OCD are sertraline and citalopram/escitalopram during pregnancy and sertraline and paroxetine during lactation
Switching from an SSRI to other drugs in treatment-resistant patients is favorable to other pharmacological options
Risperidone, haloperidol, quetiapine, and olanzapine are the most preferable antipsychotic drugs for augmentation treatment
Benzodiazepines, especially lorazepam, may be administered for a short time in pregnant or breastfeeding patients with intensive anxiety
Mirtazapine at 7.5–15 mg/day may be added to SSRIs in pregnant patients with severe insomnia, decreased appetite, and nausea/vomiting
OCD patients who are symptomatically non-remitted require prophylactic treatment during pregnancy and the postpartum period

OCD obsessive-compulsive disorder, *SSRI* Selective serotonin reuptake inhibitor

16.4 Conclusion

Due to the possible negative effects of OCD on the fetus, infant, and pregnancy, patients should be carefully monitored during pregnancy and the postpartum period. The data on treatment of the disorder are very limited, and there are no published guidelines regarding the clinical approach to OCD in pregnant and lactating women. Therefore, it is difficult to know to decide the pharmacological options for these women. Both prophylactic medication and treatment of active symptoms should be individualized based on the history of OCD, the clinical status, and the degree of impairment in social and family functions in the patient.

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Anxiety Disorders

17

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17.1 Introduction

The perinatal period, comprising conception to 1 year after birth, is a time of significant change in a woman's life. Perinatal mental illness is a significant complication of pregnancy and the postpartum period [1], affecting approximately 25% of women [2]. These disorders include depression, anxiety disorders, and postpartum psychosis. Although anxiety is often considered normal during this transitional state, high levels of maternal anxiety during pregnancy can compromise the health of both the mother and child [2, 3]. During pregnancy, the primary concerns are related to changes in the physical appearance, the delivery, and the pressures of parenting [3–5].

The reported prevalence of anxiety disorders during pregnancy has varied from 4 to 30% because of differences in study recruitment strategies and

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methodologies; meanwhile, anxiety disorders are diagnosed in 16% of women in the postpartum period [6–8]. The most common anxiety disorder before childbirth is generalized anxiety disorder (GAD), arising in approximately 10% of future mothers, followed by panic disorder (PD) in approximately 5% of expectant mothers [9–12].

Growing evidence illustrates that perinatal anxiety can lead to adverse outcomes for the health of women and their children [13–15]. High anxiety levels during pregnancy have negative effects on fetal development due to increased cortisol release from the mother and within the placenta [16].

In this text, we will discuss the treatment of anxiety disorders and the risks of untreated anxiety disorders in the perinatal period. We conducted a literature review using the PubMed database and predefined keywords such as anxiety, anxiety disorders, panic, tocophobia in pregnancy and the perinatal period, postpartum, and prenatal or postnatal.

17.2 Untreated Perinatal Anxiety Disorders: Which Risk?

Clinicians are often forced to determine whether psychiatric disorders in pregnancy should be treated pharmacologically. This problem stems from the conflicting results of studies evaluating the outcomes of psychotropic drug exposure in utero and the need for doctors to consider the well-being of both the mother and fetus.

Untreated perinatal anxiety increases the risks of postpartum depression [5], preeclampsia [17], childbirth fear [18], suicidal behavior [19], scanty coping strategies [20], and alcohol abuse [21] in mothers. In addition, perinatal anxiety is associated with negative effects on the health of the newborn, including prematurity [22], low Apgar scores [23], and increased resistance of the uterine artery with consequent low birth weight [24]. Moreover, perinatal anxiety has neurodevelopmental consequences including significant risks of emotional and behavioral disorders in offspring such as ADHD [25]. Van den Bergh and Marcoen [26] found that the children of women with high levels of anxiety in pregnancy were irritable and tended to cry excessively at 7 months of age. At 9 years old, the young boys continued to be hyperactive, exhibited attention deficits, and engaged in aggressive behaviors. Hunter and colleagues studied P50 auditory sensory gating (a putative marker of early attentional processes) in children born to mothers with anxiety, finding that the children of untreated anxious mothers have reduced P50 sensory gating compared to anxious mothers treated with antidepressants (ADs) [27]. The relationship between prenatal exposure to maternal anxiety disorders and impaired P50 sensory gating was consistent with previous studies [28] reporting that attentional dysfunction was elevated in children prenatally exposed to maternal anxiety.

These studies suggested that both maternal depression and prenatal anxiety disorders have negative consequences on child developmental outcomes. Therefore, it is important to discuss various possible treatments.

17.3 Pharmacological Treatment in Pregnancy: Current Controversies and Potential Risks for the Fetus

Selective serotonin reuptake inhibitors (SSRIs) are frequently used to treat anxiety disorders, and their use during pregnancy has increased over time. It has been estimated that up to 13% of all pregnant women use at least one AD during pregnancy, mainly SSRIs [29]. SSRI use by pregnant women ranges 2–7% in Canada and Western European countries and 5–13% in Australia and the USA.

These drugs pass through the placenta, and they are secreted in small quantities into breast milk. Studies on AD use in pregnancy are conflicting [30]. Several studies reported various consequences associated with AD use during pregnancy such as cardiac malformations, pulmonary hypertension, preterm birth, low birth weight, neural tube defects, and gastrointestinal outcomes [31]. Among papers questioning these associations, in particular cardiac malformations, one large population-based cohort study investigated 949,504 pregnant women, 64,389 of whom used ADs during the first trimester. This study, which was funded by the Agency for Healthcare Research and Quality and the National Institutes of Health, did not find a significant risk of cardiac malformations in children born to women who used ADs during the first trimester relative to unexposed women [32].

Instead, studies found that SSRI or selective serotonin-noradrenaline reuptake inhibitor (SNRI) use during the third trimester is associated with a pattern of neurobehavioral symptoms in newborns called postnatal adaptation syndrome (PNAS). PNAS is characterized by irritability, hypertonia, jitteriness, and feeding difficulties occurring at birth or within a few days after delivery. This syndrome occurs in up to 30% of infants exposed to SSRIs or SNRIs during the third trimester, and it generally resolves within days or weeks [33]. Serotonin overstimulation in the fetal brain is one proposed pathogenetic mechanism of PNAS, as suggested by the finding of significant correlations between neonatal adaptation symptoms and indicators of high central nervous system serotonin activity such as umbilical vein 5HIAA concentrations [34].

The literature also describes cases of newborns exposed to SSRIs who develop persistent pulmonary hypertension of the newborn (PPHN). PPHN is a normal condition for the fetus in utero because the placenta is responsible for gas exchange. At birth, when the lungs replace the placenta in gas exchange, there is a rapid drop in pulmonary vascular resistance with increased pulmonary blood flow. PPHN, which occurs at a rate of approximately 1–2 cases per 1000 births, can develop whenever resistance in the pulmonary blood vessels is maintained after birth, leading to poor oxygenation. It has been reported [35] that SSRI use after the 20th week of pregnancy was associated with an increased risk of PPHN (adjusted odds ratio = 4.29, 95% CI = 1.34–13.77) compared with AD nonuse. SNRI use during the same time window and SSRI and SNRI use before the 20th week of gestation were not statistically associated with the risk of PPHN.

The physiological changes occurring in mothers during pregnancy (e.g., body weight, hepatic and renal function) are known to cause changes in drug disposition, leading to differences in the proper drug dose between pregnancy and prior to

conception. A recent study in Norway [36] illustrated that the serum concentrations of paroxetine and fluvoxamine decrease to approximately half of the prepregnancy levels, whereas sertraline concentrations increase by as much as 70%. Venlafaxine, fluoxetine, citalopram, and escitalopram concentrations remain largely unchanged, and thus, dose adjustment is generally not necessary in pregnancy.

The results of studies on the effects of BDZs in the first trimester on newborns are overall inconsistent. BDZ use in late pregnancy is linked to floppy infant syndrome, which is characterized by lethargy, hypothermia, and sucking difficulties. Abstinence symptoms appear within a few days after delivery in newborns and include hyperreflexia, irritability, insomnia, bradycardia, cyanosis, and hypertonia [37]. Some studies [38, 39] suggested that neonates exposed to BDZs in late gestation are more likely to experience respiratory difficulties and require ventilatory support.

17.4 Pharmacological Treatment Strategies for Specific Anxiety Disorders: Scientific Evidence

17.4.1 General Considerations

Prescribing therapy to pregnant women with anxiety disorders is an arduous task due to the lack of univocal indications arising from research as well as ethical and legal implications.

According to NICE guidelines [40], pharmacological treatment might be a valid option for anxiety disorders during pregnancy or breastfeeding when the symptoms are moderate to severe, the anxiety is comorbid with depression, or there is a high suicidal risk.

ADs are considered the treatment of choice for women with anxiety disorders in the perinatal period. Safety data on AD use in pregnancy are extremely limited, as pregnant women are excluded from randomized control trials for ethical reasons, and therefore evidence has been derived from either case reports or uncontrolled trials. It is recommended that the prescription of a pharmacological treatment be performed by specialists in the perinatal mental health area. The decision to use a pharmacological treatment in pregnant and/or breastfeeding women should always be discussed with the woman and her partner to provide adequate information regarding the potential risks of these drugs and the consequences of untreated severe depressive/anxiety disorders. In addition, an accurate evaluation of the risk/benefit ratio should always be performed on a case-by-case basis when prescribing ADs in early pregnancy and during breastfeeding. The choice of treatment during pregnancy should be personalized, considering both the severity of the symptoms and the choices of the woman and her partner. The pharmacological prescription should be shared and should be accompanied by written informed consent for medical and legal reasons as well as to ensure a correct understanding of the risks and benefits of treatment. There are general recommendations for the use of antianxiety medication in the perinatal period that can be summarized as follows: administer

Table 17.1 Expert recommendations based on scientific evidence and clinical experience

Pharmacological treatment might be a valid option when the symptoms are moderate to severe, the anxiety is comorbid with depression, or there is a high suicidal risk
The decision to use a pharmacological treatment should always be discussed with the woman and her partner to provide adequate information regarding the potential risks of these drugs and the consequences of untreated severe depressive/anxiety disorders
An accurate evaluation of the risk/benefit ratio should always be performed on a case-by-case basis when prescribing ADs in early pregnancy and during breastfeeding
The treatment should be personalized
Administer drugs only if necessary, use the minimum effective dose, avoid the use of polytherapy, reduce the dosage in the final weeks to avoid neonatal toxicity, and monitor fetal conditions during pregnancy
The first-line agents recommended for treating anxiety disorders are SSRI, sertraline and citalopram during pregnancy, and sertraline and paroxetine during lactation
BDZs should be administered for a short time at the lowest effective therapeutic dosage in pregnant or breastfeeding

SSRI selective serotonin reuptake inhibitor, *BDZ* benzodiazepine, *AD* antidepressant

drugs only if necessary, use the minimum effective dose, avoid the use of polytherapy, reduce the dosage in the final weeks to avoid neonatal toxicity, and monitor fetal conditions during pregnancy [40]. The guidelines on perinatal anxiety disorders instead emphasize the importance of early detection of anxiety symptoms because of the proven risks of untreated anxiety in pregnancy and recommend screening tests, such as GAD-2 and GAD-7 testing, during each visit to ensure timely intervention [41] (Table 17.1).

17.4.2 Panic Disorder

SSRIs, particularly paroxetine, and extended-release venlafaxine are the treatments of choice for nonpregnant panic disorder [42]. To date, few data are available regarding the efficacy of antipanic medication in pregnancy. In a study of 16 pregnant women with panic attacks, Uguz et al. [43] examined the efficacy of low-dose imipramine (10–40 mg/day). According to Uguz [44], sertraline, citalopram, and low-dose imipramine can be used in the first-line setting, whereas other drugs should be reserved for patients who fail to respond to initial therapy.

Clinical research has demonstrated the efficacy of BDZs in rapidly controlling anxiety symptoms. In cases of agitation, BDZ should be administered on a short-term basis at the lowest effective therapeutic dosage [45].

17.4.3 Generalized Anxiety Disorder

SSRIs represent the first choice of pharmacological treatment for GAD, with a response rate ranging from 30% to 50%. Tricyclics such as imipramine are equally effective, but their safety profile is poorer, thus relegating their use to the second line

or in cases of non-response to SSRIs [46, 47]. Cognitive behavioral therapy is the first treatment option for mild-to-moderate perinatal GAD, but in more severe cases, pharmacological treatment should be considered [48]. SSRIs, excluding paroxetine, are usually used for pregnant women with GAD in pregnancy [49]. Studies have demonstrated the efficacy of SSRIs for perinatal GAD as well as their good safety profile during breastfeeding, especially sertraline, which accumulates at low levels in breast milk [50, 51].

Venlafaxine can be considered a potential treatment option in early pregnancy in women with severe GAD who previously responded to this drug [52].

17.4.4 Specific and Social Phobias

The literature on the treatment of phobias, both specific and social, during the perinatal period is extremely limited, and no studies have examined the postpartum period [53]. In recent years, attention has been focused on tocophobia, which is a severe fear of pregnancy and childbirth, a specific phobia of the perinatal period that occurs in approximately 6% of pregnant women. The intensity of this phobia can lead to pregnancy avoidance or cesarean delivery. It may be primary in nulliparous women or secondary to a previous traumatic birth or perinatal depressive disorder [54]. The paucity of literature on the treatment of tocophobia does not allow reliable conclusions regarding treatment options [55].

17.5 Conclusion

Anxiety in the perinatal period is frequent and requires attention and additional research to clarify the best strategy in the pharmacological management of this condition. Management of this condition should include also non-pharmacological options such as cognitive behavioral techniques. Exposure to drugs may be associated with risks for the fetus, but the impact of untreated disorders on child developmental outcomes should also be considered.

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Post-traumatic Stress Disorder

18

Mine Sahingoz and Serap Sari

18.1 Introduction

Post-traumatic stress disorder (PTSD) is one of the significant mental health concerns for women in perinatal period, with prevalence estimates range from 0% to 35% in pregnancy [1, 2] and from 0% to 21% in postpartum [3, 4]. The onset of PTSD may occur before the pregnancy or in the perinatal period [5]. It is possible that PTSD can be retriggered by events during pregnancy and childbirth for women with a history of trauma or prior PTSD [6]. Several studies have identified numerous risk factors that increase the likelihood of PTSD in the perinatal period, including history of trauma and psychological disturbances, trait anxiety, obstetric factors and complicated deliveries and low social support [7–9]. There is suggestive evidence that PTSD during pregnancy is associated with poor outcomes such as preterm birth [10, 11], and postpartum PTSD also is associated with bonding difficulties with their babies [12] and more intrusive behaviours towards their infants [13]. Also, treatment of PTSD during the perinatal period is very difficult because untreated PTSD may increase the risk of pregnancy complications and adverse outcome and affect infant emotion regulation and development as well as potential hazards of treatment of pregnant and breastfeeding women with psychotropic drugs [14, 15]. Unfortunately, there is not currently enough information about treatment of PTSD in the perinatal period.

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18.2 Risks of Untreated PTSD

PTSD is known to be a potentially disabling condition that can persist for decades [16, 17]. This disorder is associated with high comorbidity of psychiatric illnesses involving depression, anxiety, psychosis, personality and substance use disorders [18, 19]. It has been suggested that both PTSD and co-occurrence psychological disorders increase the emergence of high-risk behaviours such as suicidal thoughts and behaviours and alcohol/substance use in general trauma literature [20]. Although there is not adequate evidence, it should be taken into account that women with perinatal PTSD may have similar risks. Traumatic stress and PTSD during pregnancy may negatively affect birth outcomes or foetal development indirectly through risky health behaviours and poor self-care (e.g. attendance to medical care, nutrition and sleep). Furthermore, anxiety and depression may also increase risks for preterm delivery, low birth weight, and reduced foetal growth [21]. On the other hand, PTSD during pregnancy may directly predispose women to birth complications by neuroendocrine alterations, such as the dysregulation of cortisol, vasopressin and oxytocin [10, 22, 23]. There are reports suggesting that post-traumatic stress is associated with preterm delivery [10]; low birth weight [24], decrement in infant head circumference at birth [25].

Several studies reported that maternal distress may associate with an adverse impact on maternal and child health [22, 23, 26, 27] and may affect child developmental outcomes and family functioning in perinatal period [28, 29]. A large prospective study found that women with higher postpartum PTSD scores were significantly less likely to have breastfed their infant [30].

There is suggestive evidence that additional long-term impacts on families and infants include breastfeeding difficulties, as well as feelings of detachment with infant and mother, infant behaviour and cognitive development [29, 31, 32]. In addition, it has been suggested that untreated PTSD associated with sexual avoidance, secondary tocophobia (fear of childbirth), disordered maternal-child bonding or over anxious/protective parenting and maternal long-term physical and emotional health issues [12, 13, 33, 34]. Given that perinatal PTSD is related to high risk of pregnancy complications and adverse birth outcomes [35] and postpartum PTSD may have negative impact on women and the baby [36, 37], it is important to identify and treat women with PTSD in perinatal period.

18.3 Pharmacological Treatment

There is no distinctive guideline in the literature for the treatment of perinatal PTSD, despite evidence that PTSD occurs in a significant proportion of pregnant and in pregnant or lactating women and it is associated with poor outcomes such as preterm birth [10, 11]. Although insufficient data, it is presumed that treatment methods known to be effective in the treatment of PTSD may also be effective in the perinatal period. Unfortunately, there is also limited data on therapeutic interventions for PTSD non-perinatal population. The recent guidelines of PTSD treatment

recommended that psychological treatments, including trauma-focused cognitive therapy, should be preferentially used as a routine first treatment of PTSD [38, 39]. Numerous systematic reviews and meta-analyses demonstrated that the psychotherapeutic interventions including trauma-focused cognitive behavioural therapy (CBT), exposure therapy and eye movement desensitisation and reprocessing (EMDR) and debriefing and counselling are effective on the symptoms of PTSD [40–43].

Despite the fact that efficacy of pharmacological medications in the treatment of PTSD has been discussed, they are still widely used, especially, due to psychological interventions, lack of availability or failure to respond or intolerate [44]. It is likely that pharmacotherapies may provide improvement in treatment of common symptoms such as depression, anxiety and sleep problems than complete remission in PTSD [45].

18.3.1 General Considerations

Determining the appropriate psychiatric medications to use in the treatment of PTSD in perinatal period is complicated by pregnancy and breastfeeding. Principally, nonpharmacological methods should be preferred firstly in the pregnant or lactating women for treatment of PTSD. However, it is sometimes necessary to use pharmacological treatment, in patients with severe anxiety and depressive symptoms, deficiency of nutrition or disturbance of sleep [46]. A wide range of pharmacotherapy has been tested in the treatment of PTSD, but it is unclear which pharmacological treatment should be selected among all the compounds available for perinatal PTSD. The pharmacologic treatments reported to be efficacious in the literature of treatment of PTSD may be preferred according to their safety in pregnant or lactating women.

The primary concerns regarding the use of psychotropic medications during pregnancy and lactation include physical or neurobehavioral teratogenesis in the foetus, neonatal toxicity and neonatal withdrawal. Before PTSD treatment is decided, it should be evaluated conditions such as severity of depression and anxiety, risk of suicide, nutrition deficiency and sleep disturbances due to PTSD. In addition, it should be identified whether the PTSD itself or treatment of PTSD is independently associated with possible negative effects on both the mother and infant as well as potential benefits of treatment. The risks and benefits of medication use during pregnancy or breastfeeding should be weighed individually. Clinicians should inform both parents about the risks of treated and untreated PTSD. Parents and physicians must decide together for regimen of treatment.

Psychotropics should be selected with respect to evidence for both efficacy and safety in the perinatal period. If possible, psychotropics should be used at the lowest doses and short-term, and combination of medications should be avoided. Due to the pharmacokinetic changes in pregnancy, clinicians should closely monitor patients, especially during the third trimester and the antepartum period, to maintain a therapeutic blood level and to avoid toxicity.

18.3.2 First-Line Pharmacotherapy of PTSD

Most guidelines agree that serotonin reuptake inhibitor antidepressants (SSRIs) are the drugs of first choice, being backed by a large body of evidence from randomised controlled trials (RCTs) [47–49]. SSRIs often produce modest results despite they have currently the most evidence of efficacy on PTSD treatment [50]. The use of selective norepinephrine-serotonin reuptake inhibitors (SNRIs), particularly venlafaxine, is also supported by clinical guidelines [51].

There are only two medications approved for the treatment of PTSD by the US Food and Drug Administration (FDA), sertraline and paroxetine. All other medications for PTSD are considered off-label use. Paroxetine, sertraline and fluoxetine were found to be superior to placebo in treating of PTSD [52–54]. A systematic review and meta-analysis found statistically significant evidence for fluoxetine, paroxetine and venlafaxine versus placebo but no evidence sertraline in the treatment of PTSD [44]. Similarly, a recent review demonstrated evidence for the effect of paroxetine, venlafaxine and fluoxetine and less so for sertraline in the treatment of PTSD [55]. A large multinational RCT found venlafaxine was effective for PTSD re-experiencing and avoidance/numbing clusters, but not for hyperarousal [56]. Although venlafaxine demonstrated a large initial effect, this decreased over time [57]. Other SSRIs, such as citalopram and fluvoxamine, currently have far less evidence for their effectiveness in PTSD [58, 59]. Fluvoxamine showed improvement in subjective sleep quality and PTSD symptoms in a few studies [60].

To date, SSRIs are the most studied medications in pregnancy and lactation among available psychotropic drugs [61]. Paroxetine has a stronger support for the efficacy in the treatment of non-perinatal PTSD than sertraline [50]. However, paroxetine and fluoxetine are not recommended during pregnancy due to evidences suggesting increased risk of foetal defects [62, 63]. The literature shows that paroxetine and fluoxetine have the strongest association with congenital malformations and negative birth outcomes, whilst the associations between sertraline and citalopram with negative outcomes remain weaker. Therefore, sertraline may be chosen as first-line drug treatments for PTSD in pregnant women in the SSRI class [63]. Citalopram may also be preferred in pregnant women, but it has lesser evidence than sertraline for their effectiveness in PTSD. Fluvoxamine is not recommended during pregnancy because of limited data on both its safety in the foetus and efficacy in PTSD treatment [64]. Limited data on venlafaxine show that the use of venlafaxine during pregnancy does not increase the teratogenic risk [65, 66].

Several studies on antidepressants and breastfeeding indicated that paroxetine and sertraline produce lower infant plasma levels than other antidepressants, while citalopram and especially fluoxetine produce the highest plasma levels in infants. Therefore, sertraline and paroxetine should be preferred as first-line drugs during lactation period [63, 64, 67]. Among the antidepressants, sertraline seems to be the best opinion during perinatal period as it can also be continued in breastfeeding. Fluoxetine and citalopram/escitalopram are not appropriate for first-line treatments of PTSD in lactation due to the high infant exposure for these drugs. Venlafaxine and fluvoxamine should not be considered as first-line therapies because of

inadequate data on safety in lactation. However, other antidepressants except sertraline and paroxetine can be used in special cases such as a history of their effectivity or if the mother has used one of these drugs during pregnancy.

18.3.3 Second-Line Pharmacotherapy of PTSD

Second-line recommended medications generally include a less evidence of effectiveness on PTSD symptoms. Additionally, the majority of them have a greater side effect profile than SSRI or SNRI medications, for example, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

TCAs and MAOIs were the first medications tested in RCTs for treating PTSD. Despite promising results from some RCTs for TCA in PTSD, high dropout rates due to common side effects complicated the interpretation of results in these studies [68–70]. TCAs are not generally recommended in first-line treatment in guidelines. It is also conceivable that they may have value as add-on therapy to another drug or psychotherapy, as a way to enhance sleep or to resolve specific symptoms, such as dissociation and pain [71]. Phenelzine provided mixed evidence for its efficacy in treatment of PTSD [72, 73]; nevertheless brofaromine failed to produce efficacy on PTSD symptoms in two placebo-controlled trials [74, 75]. For MAOIs, the necessity of a low tyramine diet to avoid hypertensive crisis and their contraindication in combination with other antidepressants and sympathomimetics means this class also has limited use [70].

A review of the literature on the safety of TCA antidepressant in pregnancy suggests that although there is a slight increase in the rates of congenital anomalies in several studies, the majority of studies did not show any increase [76]. However, a meta-analysis has shown that exposure to TCAs during late gestation was associated with poor neonatal adaptation [77]. The use of TCAs (except to doxepin) appears to be a relatively safe option during breastfeeding [78], but there is a case of amitriptyline presenting with severe sedation and poor nutrition in the breastfed baby [79]. When the limited data on both efficacy in treatment of PTSD and safety for the maternal use of TCAs in gestation and lactation are considered, their use during perinatal period is restricted.

There is a very limited number of data on safety of MAOIs during both pregnancy and breastfeeding [80, 81]. It is recommended to avoid these medications due to dietary and medication restrictions, along with the potential to cause hypertensive crises in perinatal period [82].

Nefazodone has been shown to significantly improve the most of PTSD symptoms, including intrusive thoughts, avoidant behaviours, emotional numbing, nightmares, sleep, depression and anger, but unadvisable because of a risk of hepatotoxicity in pregnant or lactating women [57, 83]. Trazodone is one of the most commonly prescribed medications in the treatment of PTSD patients with insomnia or nightmares. There have been no RCTs to demonstrate its efficacy for sleep disturbances related to PTSD despite its beneficial effects on sleep habits [83, 84]. Mirtazapine was reported to improve PTSD symptoms and associated anxiety as well as useful

in reducing the frequency and intensity of nightmares [52, 83]. The majority of data show that mirtazapine does not increase the risk of malformation in pregnancy and is relatively reliable in lactation [85, 86]. Similarly, limited available data suggest that the use of trazodone is safe both during pregnancy due to a low risk of malformation and during breastfeeding due to a low relative infant dose [86–88]. Therefore, mirtazapine and trazodone may be used in pregnant or breastfeeding women with PTSD for treatment of sleep disturbances.

Atypical antipsychotics have also been used for PTSD if the treatment use of SSRIs does not show efficacy. The relatively large body of evidence of pharmacological treatment for PTSD indicates that atypical antipsychotics may be effective in PTSD with promising initial findings [50, 89]. The majority of studies were performed on the use of antipsychotics as augmentation agents, but less work on these medications as monotherapy [90, 91]. Whilst there are some studies that recommended antipsychotics to address comorbid psychotic symptoms/disorders or comorbid bipolar disorder in PTSD patients [92, 93], others reported that second-generation antipsychotics (SGAs) were used primarily to target refractory insomnia/sleep disturbances in patients with PTSD [94]. Currently, numerous reviews and meta-analyses found that risperidone and olanzapine generally have more evidence for both efficacies in the treatment of non-perinatal PTSD than quetiapine or aripiprazole [95].

For risperidone, there are positive results in the reduction of several PTSD symptom clusters such as re-experiencing and hyperarousal subscale scores with adjunctive risperidone for antidepressant-resistant PTSD [96]. Some placebo-controlled studies of risperidone monotherapy indicated that it may be utilised as effective in the management of PTSD [97]; in contrast, others did not [98].

Like both monotherapy and augmentation with SSRIs in PTSD patients, the use of olanzapine is supported by evidence on symptom improvement in placebo-controlled trials [91, 99]. In addition, olanzapine has also shown positive effects in improving sleep problems [91]. However, in a controlled study of olanzapine monotherapy in PTSD, the clinical response to olanzapine (n = 10) was inadequate [100]. There is limited data in the literature for the use of quetiapine in PTSD, but quetiapine is one of the most commonly prescribed PTSD anti-nightmare medications [83]. Especially, for the sleep disturbances related to PTSD, quetiapine was found beneficial in some but not all trials [101, 102]. A recent systematic review suggests that aripiprazole as monotherapy or adjunct therapy for PTSD appears to improve symptoms associated with PTSD such as anxiety, avoidance, hyperarousal, re-experiencing symptoms and quality and length of sleep [103]. A small placebo-controlled study hypothesised significantly lower PTSD and depressive symptoms in the ziprasidone versus placebo group, but researchers terminated the study because intolerable adverse effects occurred in a significant proportion of patients receiving ziprasidone [104].

There are very little data for the second-generation antipsychotic drugs, with respect to teratogenic or toxic effects on the foetus. A recent review reported that a slight increase in the rate of congenital anomalies following prenatal risperidone was observed in some smaller studies [76]. A few studies have suggested that these

agents may increase the risk of hyperglycaemia in pregnant women as well as the rate of poor neonatal adaptation [105]. However, the majority of available studies on the safety of the second-generation antipsychotics in pregnancy and lactation demonstrated that they did not increase the risk of overall deformity [76, 106]. Given the amount of clinical data on the safety in perinatal period and efficacy in PTSD treatment of the second-generation antipsychotics, it is recommended to use risperidone and olanzapine during pregnancy and olanzapine and quetiapine during lactation. There are controversial results on the efficacy of augmentation of antipsychotic with SSRIs in non-perinatal PTSD [99, 101, 103]. Moreover, antipsychotic augmentation may lead to higher adverse effects than monotherapy on the foetus or breastfed infant. Therefore, these treatments should be considered when women are unresponsive to monotherapies, and they should be used at low doses as possible.

There are various recommendations among the guidelines and treatment algorithms for antiadrenergic agents in PTSD treatment [95]. Several RCTs of prazosin observed that it had beneficial effects on nightmares and insomnia related to PTSD [107], but results have been mixed regarding its efficacy for the full PTSD syndrome [108]. Some reports recommend prazosin as the first-line pharmacotherapy in PTSD patient with sleep disturbances before SSRIs [109], while Ipser and Stein [50] recommended it for sleep and nightmares unresponsive to SSRIs. In contrast with prazosin, there have been inadequate evidences on sleep disturbances or PTSD symptoms for both guanfacine and clonidine [110, 111]. Prazosin is not recommended for use during pregnancy and breastfeeding due to insufficient data on prazosin safety, even though available limited data on use of prazosin in pregnancy do not support an association between prazosin and congenital defects [112].

Propranolol has been investigated in several studies to prevent post-traumatic symptoms and has been found useful to reduce the risk of developing PTSD if given immediately after trauma by some researchers [113] although not by others [114]. Additionally, Brunet et al. [115] found that propranolol administration during an exposure session reduced physiological hyperarousal during later re-exposure.

Propranolol has been extensively used to treat a variety of conditions such as hypertension and pheochromocytoma in the mother and tachyarrhythmias in both the mother and foetus during pregnancy, and no teratogenicity associated with this agent has been documented [116]. However, adverse foetal effects have occasionally been noted [117]. Therefore, it is only recommended for use in pregnant women with PTSD when the benefit outweighs the risk. Although no side effects have been reported in breastfed infant and propranolol levels have been determined low in breast milk, it is recommended to monitor the autonomic effects related to beta blockage in the baby during the three-hour period after breastfeeding [118, 119].

To date, there is little evidence to support the use of antiepileptics in the treatment of PTSD. Bajor et al. [109] found an evidence of the effectiveness of lamotrigine or topiramate on re-experiencing symptoms, lamotrigine on avoidance/numbing symptoms and levetiracetam on global symptoms in patients with PTSD. Several reports recommended topiramate for PTSD symptoms including nightmares [49, 83], while others did not [44]. In addition, numerous systematic reviews indicated that antiepileptics failed to achieve significance for treating PTSD symptoms [57].

Exposure to antiepileptics, including valproic acid and carbamazepine, during pregnancy is known to be associated with an increased risk of major congenital malformations [76]. Similarly, current evidence suggests topiramate may be teratogenic and may also lead to an increase in the rate of developmental problems [120, 121]. Infants who were breastfed by mothers treated with topiramate were found to have very low serum levels and no side effects [122]. Lamotrigine has a good safety profile compared with other antiepileptics, and most studies found no increase in the rate of major congenital anomalies [123]. On the other hand, it should not be forgotten that data about neurodevelopmental outcomes are rather limited. Lamotrigine is considered moderately safe during breastfeeding [124]. Given the inconclusive evidence on the efficacy of antiepileptics in the treatment of PTSD, antiepileptics are not recommended for use in pregnant or lactating women with PTSD.

Numerous systematic reviews have indicated that benzodiazepines are no benefit in PTSD although they have been prescribed commonly in patients with PTSD [44, 48, 125]. However, eszopiclone, a hypnotic drug, was found useful in only one study [126]. According to the several guidelines, benzodiazepines are contraindicated for patients with disinhibition and addiction problems [48, 127].

Recent reviews provided that NMDA receptor modulators may have potential for benefit in treating PTSD by playing a role on the glutamatergic receptor subtype NMDA in fear extinction and reconsolidation [128, 129]. However, there have been limited clinical data.

18.3.4 Prevention of PTSD After Trauma

It is estimated that up to 80% of all people will experience at least one potentially traumatic event [130, 131]. Fortunately, PTSD or other psychopathologies do not develop in the majority of people. Therefore, it is hypothesised that post-traumatic stress symptoms may be prevented in individuals exposed to trauma [132–134]. There are many approaches to PTSD prevention, the most common of which is psychotherapy. The findings of systematic reviews and controlled trials suggest that trauma-focused CBT is potentially beneficial in preventing chronic post-traumatic symptoms, when provided within 6 months of the incident [135]. Also, few evidence indicates that the use of pharmacological interventions immediately after exposure to trauma may reduce the risk of developing of PTSD [136]. Several medications such as propranolol, glucocorticoids, opioids, antidepressants, neuroleptics and salbutamol have been tested in the early aftermath of trauma with an attempt to prevent PTSD [132–134, 136].

A small randomised placebo-controlled study found that acute administration of propranolol (160 mg/day) was superior to placebo in reducing subsequent post-traumatic symptoms and physiological hyperactivity to reminders of trauma, but not the emergence of post-traumatic stress disorder, at 1 month [113]. A naturalistic study suggests acute administration of propranolol (120 mg/day) prevented the

Table 18.1 Expert recommendations based on scientific evidence and clinical experience

There are risks of untreated PTSD as well as the medication use on the foetus or infants
Before PTSD treatment is decided, conditions should be evaluated such as severity of depression and anxiety, risk of suicide, nutrition deficiency and sleep disturbances due to PTSD
Clinicians and patients are concerned about the possible risks associated with PTSD and the medications
The treatment should be individualised
Both the patients and the exposed foetus or infant should be closely monitored
Monotherapy and lowest therapeutic doses are preferred
The first-line agents recommended for treating PTSD are sertraline, paroxetine, venlafaxine and fluoxetine
According to the their safety, sertraline may preferred during pregnancy, and sertraline and paroxetine may preferred during lactation
Trazodone, mirtazapine and olanzapine are the most useful and reliable medications for sleep disturbances such as nightmares and insomnia in perinatal PTSD
Risperidone, olanzapine to a lesser extent quetiapine and ziprasidone are the most preferable antipsychotic drugs for augmentation treatment in PTSD
It is recommended to use risperidone and olanzapine during pregnancy and olanzapine and quetiapine during lactation
Propranolol can be given in pregnant and lactating women at low doses and for short periods within 48 hours after exposure to trauma
Benzodiazepines should be avoided in treatment of PTSD

PTSD post-traumatic stress disorder

emergence of syndromal PTSD at 2 months [137], but not all evidence is consistent [138, 139]. Based on scientific evidences on effectivity of propranolol for the prevention of traumatic symptoms in non-perinatal patients, propranolol can be given in pregnant and lactating women at low doses and for short periods after exposure to trauma.

Findings from controlled trials of glucocorticoids, such as hydrocortisone [140, 141], are promising and support suggestions that cortisol administration after trauma may be a useful approach in preventing PTSD [142]. But this strategy is not appropriate during pregnancy and lactation since cortisol may disrupt the hypothalamic-pituitary-adrenal axis.

While benzodiazepines are widely used in acute trauma settings, the rationale for their use in treating trauma has been undermined by the negative findings of a non-randomised controlled trial of clonazepam or alprazolam [143]. Early administration of temazepam following life-threatening incidents actually resulted in a larger proportion of participants developing PTSD in a small randomised, placebo-controlled trial [144]. There is an evidence for the efficacy of sertraline in preventing post-traumatic symptoms [145], but not for gabapentin [139] or escitalopram [59]. A small number of randomised double-blind placebo-controlled relapse prevention studies find evidence for the efficacy of longer-term treatment, for fluoxetine [53] and sertraline [52].

18.4 Conclusion

It is important to manage women with PTSD during perinatal period given that they are not only at higher risk of pregnancy complications and adverse perinatal outcomes [35] but also postpartum PTSD which may have negative impact on women and the baby [36, 37]. Nevertheless, there are no published guidelines regarding the clinical approach to women with PTSD during perinatal period. Especially, pregnant women determined to be in risk groups should be monitored closely, and necessary support should be provided. Clinicians should be considered carefully the anticipated benefits and risks of pharmacological treatment of PTSD in pregnant or lactating women, including the potential risks of harm to a developing child; therefore, treatment should be individualised (Table 18.1).

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Alcohol Use Disorders

19

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19.1 Introduction

Although alcohol use disorders (AUDs) during pregnancy and postpartum period are usually less prevalent than in non-pregnant women, the presence of alcohol use and/or abuse as well as alcohol-related behaviours may determine detrimental clinical challenges both in pregnant and/or nursing women and their foetus and/or newborns [1]. Unfortunately, there is little research information and clinical studies to date available regarding clinical decision-making and therapeutic flow chart able to give practical and ready clinical guidelines to clinicians working within mental health and drug addiction's services in the management and treatment of pregnant

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and/or nursing women affected with AUD. Furthermore, there is little evidence to support the use of pharmacological interventions for AUD during pregnancy and breastfeeding. Similarly, there are few data to manage alcohol detoxification in pregnant women, and the use of benzodiazepines (BZDs) in pregnant women is still controversial.

In general, as stated by the recent guidelines edited by the Australian Government Department of Health [2], clinicians should advise women who are pregnant or planning a pregnancy that not drinking is the safest option as maternal alcohol consumption may adversely affect the developing foetus [3]. However, clinicians could have manage AUD in pregnancy and/or breastfeeding, especially for those women with previous AUD and/or mental health problems; hence, a practical guideline in the treatment of AUD should be specifically adapted for pregnant and/or nursing women with AUD.

The present chapter aims at overviewing the epidemiology of AUDs in pregnancy and breastfeeding, the risk of major malformations and perinatal complications, with a particular focus on the foetal alcohol spectrum disorder (FASD) and foetal alcohol syndrome (FAS), and, finally, provides some clinical guidelines for the management (pharmacological and not pharmacological) of AUD both in pregnancy and postpartum period (Table 19.1).

Table 19.1 Expert recommendations based on scientific evidence and clinical experience

Clinicians should advise women who intend to plan a pregnancy to discontinue alcohol consumption, as there is a good-quality evidence that drinking excessive amounts of alcohol during pregnancy may damage foetal development
Clinicians and researchers do not still know the minimum or threshold level at which alcohol begins to pose a significant threat to pregnancy; hence, it is preferred not using alcohol at all
Clinicians should know that alcohol is a teratogen agent; therefore, it should be avoided during pregnancy, especially during the first trimester
The likelihood of developing foetal malformations increases with increased volume and frequency of alcohol consumption during the first trimester; hence, it is preferred not having binge or heavy drinking during this period
A screening assessment for alcohol consumption, specifically designed to pregnant and/or nursing women, may help clinicians, to adopt preventive tools and provide advices to stop alcohol consumption and therapeutic strategies for the management of AUD
After identifying pregnant and/or nursing women at risk of AUD, clinicians should suggest involving a drug and/or alcohol specialist in counselling and care
AUD during pregnancy may contribute to an increased risk of congenital malformations or later intellectual disability
AUD during pregnancy may contribute to the onset of FASD
Pregnant women should be given priority access to withdrawal management and treatment

19.2 Epidemiology

According to the National Survey on Drug Use and Health [1], around 8.5% of pregnant women in the United States consumed at least one alcoholic drink in the previous 30 days, 2.5% drank five or more drinks (aka *binge drinking*) during one episode in the previous 30 days and 0.3% had five or more drinks on the same occasion five or more times (aka *heavy drinking*) in the last 30 days. However, overall pregnant women appear to consume less alcohol, compared to non-pregnant women (8.5% vs 55.1% drank at least once in the last 30 days; 2.5% vs 24.5% reported binge drinking; 0.3% vs 5.3% reported heavy drinking) [1]. According to a Norwegian population-based study which surveyed nearly 1500 women, 85% of the sample reported to have modified their alcohol consumption upon learning of their pregnancy, declaring that the primary reason was to ensure foetal well-being [4].

However, even though the alcohol consumption appears comparably lower in pregnancy than non-pregnant women, it is mandatory to reflect and evaluate that this may be valid mainly for healthy women, but for pregnant and/or nursing women affected with untreated mood and/or anxiety disorders, alcohol consumption may represent a desperate attempt to self-medicate themselves [5]. Furthermore, the risks for adverse pregnancy outcomes are much higher in women with psychosis during pregnancy than in nonpsychotic women, which is thought to be due to uncontrolled harmful factors such as nicotine, alcohol and substances of abuse amongst psychotic patients [6].

19.3 Risk of Congenital Major Malformations and Perinatal Complications

The French paediatrician Paul Lemoine firstly characterized alcohol as teratogen in 1967, by describing 127 cases of similar abnormalities amongst children born from mothers affected with ‘chronic alcoholism’ [7, 8]. Subsequently, Jones and Smith better defined the specific spectrum of dismorphologies associated with AUD during pregnancy [9]. The terminology *foetal alcohol syndrome* (FAS) was coined by Jones and Smith to describe the pattern of foetal malformations reported amongst newborns of women who took alcohol in pregnancy. The FAS is characterized by craniofacial, limb and cardiovascular defects associated with prenatal-onset growth deficiency and development delay [9]. Subsequently, it was better characterized as well other not-full FAS spectra, the so-called foetal alcohol spectrum disorders (FASDs), i.e. a pattern of dismorphologies which include as well not-fully represented clinical manifestation of FAS. FASD may include a low birth weight, preterm birth, small for gestational age, spontaneous abortions, behavioural problems, developmental delay and cognitive deficits, related to dose-response pattern to alcohol use during pregnancy [10–15].

Foetal alcohol spectrum disorder (FASD) is an umbrella term describing the range of developmental deviations, such as craniofacial maldevelopment or neurodevelopmental abnormalities that can occur in an individual whose mother consumed alcohol during pregnancy [16]. The extent of developmental abnormalities appears to depend on the amount, pattern and timing of the prenatal alcohol exposure. However, other factors, including genetic, epigenetic and social environmental factors, may also influence the development and manifestations of the disabilities [17]. The prevalence rates for FASD have been reported to be 2–5% in the United States, 2–6% in Italy and as high as 14–21% in South Africa [18–20]. Most children affected with FASD may experience difficulties in daily life, e.g. deficit in motor control, eyesight, hearing, attention, concentration and impulse control [21]. Furthermore, it has been well-documented to have a potential relationship with the occurrence of autism, attention-deficit-hyperactivity disorder and intellectual disability [22].

The most well-known term within FASD spectrum is represented by the FAS, which is an established diagnosis ascribed to individuals who fulfil specific criteria, such as facial dismorphologies, growth inhibition and disfunction of the central nervous system [16].

A summary of FASD diagnostic process has been provided in Table 19.2.

Table 19.2 Criteria for FAS and partial FAS

1. Evidence of prenatal or postnatal growth impairment, in at least one of the following (FAS only)	• Birth weight or birth length at or below the tenth percentile for gestational age • Height or weight at or below the tenth percentile for age • Disproportionately low weight-to-height ratio at or below the tenth percentile
2. Simultaneous presentation of the following facial anomalies at any age (FAS all three, partial FAS any two)	• Short palpebral fissure length (2 or more SDs below the mean) • Smooth or flattened philtrum (rank 4 or 5 on the lip-philtrum guide) • Thin upper lip (rank 4 or 5 on the lip-philtrum guide)
3. Evidence of impairment in three or more of the following CNS domains (FAS, partial FAS and ARND)	• Hard and soft neurologic signs • Brain structure • Cognition (IQ) • Communication • Academic achievement vi. memory • Executive functioning and abstract reasoning • Attention deficit/hyperactivity • Adaptive behaviour • Social skills • Social communication
4. Confirmed maternal alcohol exposure (partial FAS)[a]	

SD standard deviation, *CNS* central nervous system, *IQ* intelligence quotient
[a]FAS can be diagnosed without this if (1) to (3) are all present

19.4 Screening Tools for AUD During Pregnancy

Nowadays, clinicians own several empirically validated screening tools for AUDs such as the CAGE [23]; the Alcohol Use Disorders Identification Test (AUDIT-C) [24]; the Michigan Alcoholism Screening Test (MAST) [25]; the Tolerance, Worried, Eye-opener, Amnesia, K/Cut-down attempts (TWEAK) [26]; and the Tolerance, Annoyance, Cut-down attempts, Eye-opener (T-ACE-R3) [27]. However, several of these screening tools were not specifically developed for pregnant women (e.g. CAGE and MAST) and were designed to pick up alcohol use patterns more common amongst men, especially alcohol dependence. Hence, they may be less effective in identifying problem in drinking amongst women, especially amongst pregnant and/or nursing women. Therefore, positive cut-off scores for alcohol use disorder screening tools need to be set differently for women than for men, since compared to men, women usually experience higher blood alcohol levels at identical exposures (doses) and women are more susceptible to end organ damage resulting from alcohol [28–30].

19.5 Pharmacological Management of Alcohol Use Disorders During the Perinatal Period

AUD during pregnancy may contribute to an increased risk of congenital malformations or later intellectual disability [31, 32] as well as an increased risk of FASD [21, 33]. There is limited evidence regarding the potential risks related to the pharmacotherapy to an exposed foetus or infant [34]. However, the risks to the foetus are likely to be greatest during the first trimester [35]. The American Psychiatric Association [36] recommends that for pregnant or nursing women with AUD, pharmacological treatments not be used unless treating acute alcohol withdrawal with BZDs or unless a co-occurring disorder exists that warrants pharmacological treatments (*Statement 14, 1C recommendation*).

Currently, there are three medications approved for the treatment of AUDs by the Food and Drug Administration (FDA) in the United States, e.g. naltrexone, disulfiram and acamprosate. Data coming from animal studies are not available for disulfiram but suggested a moderate risk for use of naltrexone and high risk for acamprosate and a possible risk for use of gabapentin and topiramate [34]. Regarding the breastfeeding, even though limited data is available, there may be potential for toxicity with disulfiram, naltrexone and topiramate [34], whereas acamprosate and gabapentin are noted to be ‘probably compatible’ with breastfeeding [34].

Naltrexone is a mu opioid receptor antagonist that has been shown to decrease the risk of heavy drinking to 83% of the risk in placebo groups and decrease drinking days by about 4% [37]. Naltrexone is available in both oral and long-acting injectable formulations. However, there are no published studies on the safety or efficacy of either formulation of naltrexone for use in AUD in pregnant women. Naltrexone is classified as a category C medication by the FDA, meaning that animal studies have shown adverse effects on the foetus, but there are no adequate

studies on reproductive effects and safety in human pregnancy [38]. A retrospective cohort study of birth outcomes in neonates exposed to naltrexone in utero reported that naltrexone-exposed neonates were generally not significantly different to buprenorphine-exposed neonates ($n = 124$) but significantly lower rates of neonatal abstinence syndrome (7.5% vs 41.8%) and shorter hospital length of stay (5.5 vs 8.0 days) in naltrexone-exposed neonates. Compared with the control group of neonates ($n = 569$), naltrexone-exposed neonates were not significantly different in terms of overall rates of congenital anomalies, stillbirths and neonatal mortality. However, naltrexone-exposed neonates were significantly smaller (3137.1 vs 3378.0 g), spent more time in hospital following birth (5.5 vs 4.3 days) and had higher rates of NAS (7.5% vs 0.2%) [39].

Disulfiram (an aldehyde dehydrogenase inhibitor that results in a severe reaction when alcohol is consumed concurrently with it, resulting in a strong deterrent effect) is also a category C medication. There is some evidence, albeit inconsistent, that exposure to disulfiram in the first trimester may increase the risk of foetal malformations [40–42]. Furthermore, the intensity of the disulfiram-alcohol reaction, which can involve severe acute autonomic instability, including hypertension, can also be considered a risk to the pregnant woman and her foetus, although there have been no studies specifically assessing the magnitude of this specific risk.

Acamprosate, which is believed to exert its action through modulation of glutamate neurotransmission thereby reducing post-acute withdrawal symptoms and consequently helping to maintain sobriety, is also a category C medication [37]. Animal data suggest possible teratogenic effects of acamprosate, but there are no human trial data to support this evidence.

Regarding the onset on an alcohol withdrawal (i.e. tremor, restlessness, tachycardia, hyperthermia, hallucinations, hypertension) in those women who abruptly stopped alcohol consumption during perinatal period, it has been documented that it may determine deleterious effects on mother and foetus (i.e. low birth weight and preterm birth) and should be treated by an activation of GABAergic system through the administration of barbiturates and/or benzodiazepines. Therefore, more data on safety and tolerability of BZDs in perinatal period may be found in Chaps. 11 and 12.

19.6 Conclusions

Overall, alcohol is a known teratogen, and its use during pregnancy can result in a host of major physical, psychological and cognitive problems, many of which are subtle and not yet well-characterized. However, the dose at which the risks to foetal development rise is uncertain. Moreover, it should be noted that no data suggest any *beneficial* effects on foetal or maternal health or development posed by alcohol use during pregnancy.

It seems that social norms can have a positive impact on women's decisions to drink or not during pregnancy (*primary prevention*). Hence, allowing abstinence-only public health recommendations to further integrate into the social and cultural norms

may, in time, further decrease rates of maternal alcohol consumption. Moreover, having clear governmental guidelines on the matter may also reduce clinician confusion about how to best advise women of the risks of alcohol use during pregnancy.

Regarding the pharmacological management of AUD in pregnancy and breastfeeding, there are no conclusive and definitive clinical guidelines, and the only three drugs, currently approved by FDA, for the management of AUD in general, have not been clinically tested, mainly for ethical reasons, to pregnant and/or nursing women. Therefore, when deciding whether to use a medication to assist in the treatment of an AUD in a pregnant woman, the risks posed using alcohol itself must be carefully weighed against the risks of the medications themselves. Therefore, it is recommended that nonpharmacological interventions should be used preferentially for treating AUD during pregnancy. For women who become pregnant while taking a medication to treat AUD, the risk of continuing or stopping pharmacological medication should be carefully individualized to the patient and discussed with the patient, her obstetrician and, if applicable, her partner. Potential risks to the foetus from medication should be balanced against the risk of relapse to AUD, which itself carries teratogenic risk (during the first trimester) and/or perinatal complications (during the second and third trimester).

Regarding breastfeeding and use of pharmacological drugs for AUD, it also requires an individualized discussion with the woman and the infant's paediatrician in balancing the benefits of breastfeeding and potential harms of exposure to medication in breast milk.

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Substance Use Disorders

20

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20.1 Introduction

Epidemiological studies demonstrated that substance use disorders (SUDs) during pregnancy are increasing amongst women of childbearing age, for both the so-called 'legal' and illegal substances [1]. Overall, it has been estimated that maternal smoking ranges between 20% and 30% [2, 3], being more likely cigarette smokers during their first trimester (around 22.9%) compared to second (14.3%) and third (15.3%) trimesters [3]. It has been well-documented, for instance, that cigarette smoke contains many potentially hazardous agents, i.e. carbon monoxide, nicotine, polycyclic aromatic hydrocarbons and heavy metals [4, 5]. Maternal smoking

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during pregnancy has been associated with abnormal development of the central nervous system [6] and behavioural problems in the offspring [7, 8]. Furthermore, caffeine is approximately consumed by 75%–93% of pregnant women [9, 10], even though inconclusive and contrasting data have been collected regarding the correlation (if any) between caffeine intake during pregnancy and offspring neuropsychiatric outcomes [11].

The National Survey on Drug Use and Health [12] reported that 5.9% of US pregnant women aged 15–44 were current illicit substance users based on data averaged across 2011 and 2012, compared to 10.7% of women in this age group who were not pregnant. Cannabis use in pregnancy has been estimated ranging between 3% and 10% of pregnant women [13]. Each year there are as many as 30,000 pregnant women using opioids in Europe [14]. For European pregnant women, a prevalence rate of 3.1% of cocaine use is reported from the 'Meconium Project' [15]. Overall, in SUDs, it has been frequently reported more than one licit or illicit substance abused. Therefore, polysubstance use may furtherly complicate the evaluation and analysis of epidemiological data collected and the outcomes of SUDs in pregnancy. For example, in the UK, 17,856 pregnant women were screened for illicit drug use. Out of 168 (0.9%) consumed illicit drugs during pregnancy, 61.3% showed illicit polysubstance use, and almost all women (97%) used multiple drugs if alcohol and tobacco were included [16].

Pregnant women affected with SUDs may have psychiatric illnesses, histories of previous and/or current physical and/or sexual abuse, a family dysfunction and a low frustration tolerance coupled with a chaotic lifestyle which may determine detrimental foetal and neonatal outcomes, behind the consequences directly correlated with the substance abused/misused. A newborn exposed to a nursing woman with SUDs may own an ineffective/poor parenting, failure to thrive, child neglect, child abuse, abandonment, etc. The Epidemiologic Catchment Area study reported that around 72% of SUD users present at least one comorbid psychiatric disorder [17]. Polysubstance use is associated with the highest rates of psychiatric comorbidity [18]. For instance, most opioid-dependent women suffer from psychiatric comorbidities (56–73%), mainly affective disorders, post-traumatic stress disorder (PTSD) or personality disorders [19–21]. A 12-month prevalence of 29.7% for mood and anxiety disorders, mainly major depressive disorder (MDD) in 15.4%, has been found amongst women with SUDs [22]. Furthermore, women with a history of depression before or during pregnancy with a concomitant history of SUDs represent a high-risk category for postpartum depression [23]. In addition, some epidemiological data reported that 3–59% of SUD-dependent women show a concomitant diagnosis of PTSD [24]. Therefore, a careful identification of risk factors and a balanced management of SUDs amongst pregnant and nursing women should be carried out by clinicians of women's mental health, in order to better clarify (if any) a primary or secondary psychiatric symptomatology, as well as choose the best management of SUD (with or without a comorbid psychiatric disorder), in order to treat and protect the mother-infant dyad.

20.2 Cannabis/Cannabinomimetics in Perinatal Period

Cannabis sativa L. (aka *canapa*, *Indian canapa*, *marijuana*, *Mary Jane*, *hashish*, *pot*, *herb*, *Maria*, *hagga*, *puf*, *maconha*, etc.) is the most commonly used illegal drug, mainly amongst the young women in Western societies [25]. It has been documented a greater recreationally consume as well in pregnancy [26]. Cannabis use during pregnancy has increased from 35% to 72% over the past decade [27, 28] and is indisputably the most common illicit drug used by pregnant women [28, 29]. Most of them used it in the therapeutic management of pregnancy-related nausea and vomiting, even though obstetrical/gynaecological effects on mothers and foetus are still not completely clarified and still need further investigation [27].

Cannabis passes placental transfer to the foetus [30], and its levels can be detected in the cord [31] with levels which are proportionately smaller than does the mother [31]. In urine samples of neonates, significant levels of cannabis have been detected [32].

In utero exposure to cannabis during the peri-conceptional period (i.e. 1–4 weeks of gestation) has been associated with an increased risk for anencephaly, whilst cannabis use in the second and third trimesters of the peri-conceptional period was not associated with an increased risk of anencephaly [33].

Pregnancy complications have been reported following the use of cannabis amongst pregnant women, including a shorter gestational period, dysfunction/precipitate delivery, low birthweight and reduced birth length and head circumference of the newborn [28, 34–36]. Furthermore, cognitive, motor and social dysfunctions and neurobehavioural complications have been demonstrated in the offspring [34, 35, 37–40].

Furthermore, exposure to cannabis during pregnancy could be associated with a plethora of neuropsychiatric disorders, including visual alterations, mental/motor and neurobehavioural disorders, aggressive behaviour and attention deficits, lower scores in verbal and memory domains and lower performance at intelligence tests [39, 41–47]. In addition, children and adolescents exposed to intrauterine cannabis are more likely to develop executive dysfunctions and worst school performances, higher rates of depressive and anxiety symptoms and development of psychiatric disorders and behavioural/addictive disorders [48–50].

Finally, the recent emergence of synthetic cannabinomimetics (aka ‘spice’ products/synthetic cannabinoids) [51] is developing a further challenge in assessing women at risk and in managing the pregnancy, mother’s mental health and foetal consequences (for a comprehensive review, see Orsolini et al. [36]).

20.3 Psychostimulants in Perinatal Period

In the late 1980s and early 1990s, cocaine dependence was labelled an epidemic by the US government, with 30% of young adult women reporting recent use [52]. Cocaine use during pregnancy received considerable media attention, when photographers documented the first newborns exposed to crack/cocaine in utero (then

renamed 'crack babies'), substantially affected by significant cognitive and psychomotor deficits as well as developmental delays [53]. Cocaine acts on the central nervous system primarily through inhibition of dopaminergic reuptake but also through activation of noradrenergic and serotoninergic sites in the basal forebrain and cerebral cortex [54]. Neurotoxic effects of foetal cocaine exposure can be manifested in foetal and long-term growth outcomes, as well as structural abnormalities, reflecting altered central nervous system development. Although some early case reports suggested an increase in major and minor congenital abnormalities amongst cocaine-exposed infants, two large prospective studies have not found an increased number of major or minor abnormalities or a consistent phenotype of abnormalities for cocaine-exposed infants or children [55, 56]. Overall, all studies of birth outcomes of cocaine-exposed neonates have identified poorer foetal growth outcomes, including lower birthweight and decreased length and head circumference, often with inversely linear relationships to the amount of drug exposure [57–59]. In a further study by Bada et al. [60], prenatal cocaine exposure was associated with an increased likelihood of low birthweight (OR = 3.59), preterm birth (OR = 1.25) and intrauterine growth retardation (OR = 2.24). Higher rates of psychopathological symptoms (e.g. depression, anxiety, psychosis and paranoia) amongst cocaine-using women were reported by [61], which were associated with higher levels of reduced head circumference and birthweight. A dose-response correlation between a prenatal cocaine exposure and a lower height and weight-for-height *z* scores at 6 years has been reported by Minnes et al. [56]. Several large longitudinal prospective cohort studies reported stable negative effects on language skills in cocaine-exposed infants and children up to 7 years of age, beyond the effect of the home environment or other confounding factors [62–64].

Despite the increasing use, particularly regarding the most popular synthetic amphetamine derivatives MDMA (3,4-methylenedioxy-N-methylamphetamine; aka 'ecstasy') and methamphetamine ([2S]-N-methyl-1-phenylpropan-2-amine; aka 'meth', 'ice', 'crystal'), there are limited safety data on stimulant use in pregnancy [65, 66]. However, as MDMA and methamphetamine are more predominant in party/rave settings and such parties are less likely to be attractive to women once pregnant, then levels of the use of these drugs are likely to be declined. However, early in pregnancy, priori to confirmation that they are pregnant, many young women will still be attending parties and may take a range of recreational substances. Thus, the prevalence of MDMA and methamphetamine use in pregnant women in early pregnancy could be high. The DAISY (*Drugs and Infancy*) Study reported that 35% of mothers who used MDMA at some point in their life before pregnancy also used MDMA in the first trimester and of those mothers who had used amphetamines in their lifetime, 9% used them at some point in the first trimester. However, only 4% of pregnant women used MDMA in the second and third trimesters [67]. The DAISY study as well reported that most MDMA users also took cannabis and that the majority of women who used MDMA in the first trimester also drank, smoked or used cannabis in pregnancy, with around a third of the women continuing to use cannabis throughout all three trimesters [67].

MDMA is a so-called 'synthetic' amphetamine. It is a powerful, indirect, monoaminergic agonist which inhibits the reuptake and promotes the release of serotonin and, to a lesser extent, dopamine. It also may determine structural changes in adult recreational MDMA users. Chronic MDMA use may lead to everyday and prospective memory impairment, frontal executive processing, problem-solving, decision taking and social and emotional intelligence impairment [68–71]. The cognitive and social deficits may in turn determine adverse parenting, possibly leading to reduced child-focused attention, poorer verbal and nonverbal communication, reduced sensitivity to the communications of their infants and higher risk of confusion or cognitive overload that could have a further impact on effect and mood of infant.

Amphetamine is a powerful stimulant of the central nervous system which may cause wakefulness, alertness, mood elevation, elation and euphoria, with effects similar to cocaine. Methamphetamine is an altered form of amphetamine with the addition of a methyl group. It is more readily absorbed into brain tissue than amphetamine [72]. Methamphetamine is generally more tolerated at higher doses and, overall, is more addictive than amphetamine. Similarly, data suggested that structural changes may occur in adult recreational methamphetamine users in specific neural pathways, specifically in dopamine-rich fronto-striato-thalamo-cortical loops [73]. Methamphetamine may have specific effects on episodic memory, executive function, speed of processing, motor skills, language, visuo-constructional abilities and further fronto-striatal and limbic-related functioning [74].

Overall, there are limited data on foetus and infants of women exposed to MDMA and/or amphetamines during pregnancy. Most data coming from animal studies which examined the outcomes after maternal MDMA and/or amphetamines are used during pregnancy. Animal studies reported an increased mortality, retinal eye defects, cleft palate, rib malformations, decreased physical growth and delayed motor development. There are only isolated reports of cardiac defects, cleft lip and biliary atresia after amphetamine in utero exposure in human infants, a reduced growth and increased foetal distress [75–80]. There is some suggestive, but inconclusive, evidence that MDMA use by mothers may have an impact on early cardiac and limb formation [81]. Regarding the long-term neurobehavioural outcomes in human infants exposed to MDMA and methamphetamine in utero, it is supposed to postulate that children exposed may be more likely to perform poorly on overall measures of cognition, language, emotional functioning and behavioural competence and may show differences in motor skills [82]. Infants exposed to methamphetamine in utero were 3.5 times more likely to be small and to have lower birthweight for gestational age, even controlling for tobacco and alcohol effects [83]. Methamphetamine exposure in the first trimester seems to be related to lower arousal, more lethargy and elevated stress indicators (those behaviours that are also typically related to abstinence (withdrawal in opiate-exposed infants)). Methamphetamine exposure in the third trimester is related to poorer quality of movement [83].

20.4 Opioids/Oppiaces in Perinatal Period

A large cohort study involving pregnant women who use prescription opioids reported a 30–60% increase in the risk of neonatal drug withdrawal associated with co-exposure to other psychotropic drugs compared with opioids alone [84]. In utero co-exposure (opioids and psychotropic drugs) increases the severity and duration of neonatal withdrawal symptomatology [84–87]. A chronic untreated addiction to heroin in pregnancy has been associated with lack of prenatal care, increased risk of foetal growth restriction, abruptio placentae, foetal death, preterm labour and intrauterine passage of meconium [88]. Furthermore, an untreated opioid use disorder has been associated with engagement in high-risk activities, such as prostitution, trading sex for drugs and criminal activities. Long-term outcomes of infants with in utero opioid exposure have been evaluated in several observational studies, reporting no significant differences in cognitive development between children up to 5 years of age exposed to methadone in utero and control groups matched for age, race and socioeconomic status, although scores were often lower in both groups compared with the general population [89].

The safety of opioids during early pregnancy has been evaluated in several observational studies. Earlier reports have not shown an increase in risks of birth defects after prenatal exposure to oxycodone, meperidine and propoxyphene [90, 91]. Whilst an association between first-trimester use of codeine and congenital abnormalities has been reported in some studies [92, 93] but not in others [94, 95], an observational study found a possible association between the use of opioids during the first trimester and neural tube defects, although not with codeine use specifically [96]. However, the observed birth defects remain rare and represent a minimal increase in overall absolute risk. Overall, concern about a potential small increased risk of birth defects associated with opioid agonist pharmacotherapy during pregnancy should be weighed against the clear risks associated with the ongoing misuse of opioids by a pregnant woman.

20.5 Pharmacological Management of Substance Use Disorders During the Perinatal Period

In general, substance-dependent pregnant women should be optimally treated with a multidisciplinary and multi-professional approach with treatment being tailored individually to the kind of substance dependence [97] (Table 20.1).

There is currently no accepted pharmacological treatment specific to cannabis use disorder [98]. In pregnant women, symptoms of withdrawal from cannabis use are usually milder and may include sleep disturbance, irritability, loss of appetite, restlessness, nausea and cramping [99, 100]. Overall, evidence recommends that pregnant women quit cannabis use, even though clinical experience suggests that for some women this may not be possible without additional support. To our knowledge, trials of medications to alleviate withdrawal symptoms from cannabis use in pregnant women have not been published. To date, dronabinol has been the

Table 20.1 Expert recommendations based on scientific evidence and clinical experience

• All patients who are pregnant or may become pregnant should be offered regular screening for alcohol, tobacco and other non-medical drug use and engaged in discussion about the risks of SUDs during pregnancy and how to reduce them
• Substance use screening should be included in the first prenatal assessment and conducted periodically throughout pregnancy and postpartum when clinically relevant and necessary. The urine drug testing is typically the preferred drug screening method
• Establishing a trusting, collaborative and empowering relationship and alliance with pregnant women affected with SUDs (with and/or without a concomitant psychiatric disorder)
• Clinicians should obtain a thorough record of current prescribed medication use and be mindful of the maternal and neonatal risks associated with the concurrent use of substances and other psychotropic drugs during pregnancy
• As SUDs may be associated with a high prevalence of trauma (i.e. sexual and physical abuse), clinicians involved in the care of pregnant patients with SUDs should be familiar with the principles of trauma-informed practice (e.g. trauma awareness, safety and trustworthiness, choice, collaboration and connection, strengths-based approaches and skill building)
• Treatment and management of pregnant women with SUDs do not only take into account a strictly substance-focused approach, by considering and improving long-term outcomes for the mother-infant dyad as well (e.g. assessing motivation and exploring ideas for change; developing a holistic treatment plan, not only medical but also social; promoting strategies for managing stress; considering nutritional asset, housing and security needs, etc.)
• Clinicians should as well give to pregnant women with SUDs the access to harm reduction supplies and services available to the general population, as it may significantly reduce substance use-related harms, including HIV and hepatitis C infection and overdose death, and improve neonatal outcomes (i.e. fewer preterm births, higher birthweights, etc.)
• Depending on the substance and diagnosis (e.g. high-risk use, substance use disorder), treatment may involve pharmacotherapy and/or appropriate referrals to specialist care as required or requested
• An individualised and integrated approach is essential to fostering stability and improving treatment and pregnancy outcomes

medication most extensively investigated. Dronabinol has been assigned by the Food and Drug Administration (FDA) to pregnancy category C, i.e. animal studies gave revealed evidence of decreased maternal weight gain and decreased number of offspring and increased foetal mortality and early foetal resorptions. Cognitive-behavioural therapy, motivational enhancement and contingency management therapies have been demonstrated to be effective for reducing cannabis use in women, even though they have not been specifically studied amongst pregnant women.

Regarding cocaine, no pharmacological therapies have been labelled evidence-based practices, and administration of medications to a pregnant woman would require extensive safety and efficacy testing. The most promising interventions identified through the Clinical Trials Network and other research groups have been psychosocial interventions (e.g. cognitive-behavioural therapies, community reinforcement approach, seeking safety, motivational interviewing, etc.) [101].

Many amphetamine and MDMA users are potentially at risk of being deeply entrenched in a drug-using lifestyle, prioritising drug-using behaviours over their own health and social needs, including baby's needs [102]. As there are currently

no replacement therapies for amphetamine dependence, the pregnant amphetamine user must be encouraged to moderate and cease drug use, but this may be an unrealistic expectation. A priority in prenatal care for the known amphetamine user is to ensure that she has adequate shelter and nutrition, that co-existing psychiatric morbidities are optimally treated and that she is encouraged to attend regular antenatal care, which is, unfortunately, even less frequent than another known drug user [103].

The first-line treatment for opioid-dependent pregnant women is opioid maintenance therapy (OMT) with methadone or alternatively buprenorphine [104]. It has been well-documented and demonstrated that OMT may outweigh any neonatal risks associated with opioid agonists [105]. OAT may eliminate or substantially reduce non-medical opioid use and associated health risks, leading to improved neonatal outcomes in comparison to untreated opioid use disorder and/or rapid withdrawal management [106, 107]. Although methadone represents the most frequently prescribed OAT during pregnancy, a growing scientific evidence supports the equal efficacy and potentially superior safety of buprenorphine and buprenorphine/naloxone for the treatment of opioid use disorder in pregnancy [106, 108–111]. However, unless clinically indicated, transitioning between methadone, buprenorphine/naloxone and slow-release oral morphine is not advisable for pregnant women stable on one of these agents during pregnancy and postpartum period, as reducing and titrating medication dosage during transition may determine a re-emergence of withdrawal symptoms and increase risk of relapse [105]. The continuity of care and adequate suppression of withdrawal symptoms during pregnancy represent the most important factors associated with improved maternal and neonatal outcomes [112, 113].

20.6 Conclusion

Although obtaining clear and accurate prevalence data on SUDs in pregnancy remains extremely complex primarily due to the stigma and prejudice against pregnant women who use substances, it is widely recognised that SUDs in pregnancy and perinatal period should be early individualised and carefully managed and treated in order to protect and adequately treat the dyad mother-foetus/mother-newborn.

Overall, all substances of abuse may variably diffuse across the placenta during pregnancy. Thus, the foetus may be exposed to substances of abuse and their potential complications. Risks of substance exposure may include organ malformation (teratogenicity), obstetrical complications (i.e. preterm delivery, low birth rate, delivery complications, low Apgar score), perinatal syndromes (i.e. neonatal toxicity which includes behavioural symptoms appearing immediately after birth such as jitteriness) and long-term postnatal behavioural sequelae (behavioural teratogenicity) [114].

Most women reported a previous cannabis use before conception with a consequent cessation after discovering pregnancy, mainly during the first or early second trimester [36]. Cannabis use may be a risk factor for pregnancy-related morbidity and mortality [115–118]. However, studies on its association with obstetric

morbidity and teratogenic effects are not conclusive, with many relying on self-report and showing inconsistent results when controlling for potential confounding factors ([34, 115–118, 119).

Although studies are limited, there is some emerging evidence for the teratogenic effects of MDMA and methamphetamine. MDMA and methamphetamine exposure is likely to occur predominantly in the first trimester, and the exposure is unlikely to occur in isolation but rather alongside other drugs.

Regarding the opioid use during pregnancy, in addition to the risks of overdose and infection, it has been reported an increased likelihood of adverse obstetrical outcomes (e.g. foetal growth restriction, neonatal opioid withdrawal, foetal demise, etc.) [120].

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Sleep Disorders

21

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21.1 Introduction

The perinatal period is often a time of sleep disturbance and deprivation, even for those with no history of sleep problems. Physical changes, significant changes in a woman's hormone profile, and the demands of caring for a newborn all contribute to poor sleep. Women in the perinatal period are at heightened risk of developing sleep disorders, such as obstructive sleep apnea (OSA) and insomnia, or for the exacerbation of pre-existing conditions. Given the relationship between disturbed sleep quality and quantity during the perinatal period and adverse maternal, fetal, and pregnancy outcomes, it is crucial that obstetricians and gynecologists, as well as primary care physicians, inquire about sleep to determine if further investigation or treatment is warranted.

21.1.1 Sleep in Pregnancy

Sleep disruption during pregnancy is very common, with most women reporting a worsening of sleep quality and a significant increase in night awakenings from pre-pregnancy levels [1–3]. Contributing factors include hormonal changes, fetal movement, bladder distention, gastrointestinal discomfort, nausea and vomiting, and temperature fluctuations. Early in pregnancy there is a significant increase in the

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secretion of progesterone, which can cause nocturnal sleep fragmentation, as well as exerting an inhibitory effect on smooth muscle, increasing nocturnal urinary frequency and heartburn [4]. This effect on the smooth muscle can also result in increased snoring and risk of obstructive sleep apnea (OSA) and restless legs syndrome (RLS), also known as Willis-Ekbom disease, in some women [5, 6]. These interruptions, as well as those caused by nausea, vomiting, and anxieties about the pregnancy, fetus, and delivery, can result in a significant loss of sleep.

The second trimester usually sees the least severe disruption of sleep, largely due to the leveling off in the secretion of some hormones and modest fetal size. However, sleep quality is still far from pre-pregnancy norms. As the fetus grows, the diaphragm is restricted, and breathing becomes shallow. Progesterone and estrogen levels steadily increase over the second and third trimesters [7, 8]. The rise of both hormones is thought to contribute to insomnia [9], and estrogen can lead to congestion of the nose and disrupt breathing during sleep, increasing the risk and severity of OSA [10–12]. Fluctuations in estrogen, progesterone, and prolactin have been proposed as potential causes of RLS [13], although this is contested [14, 15].

The third trimester is associated with the greatest changes in a pregnant women's sleep. Estrogen levels continue to rise in this trimester, leading to increased upper-airway mucosal congestion and up to a 40% increase in maternal blood volume [16, 17], contributing to pregnancy rhinitis and increasing the likelihood of snoring and OSA [18–20]. Women who are overweight or obese and/or who experience significant fluid retention during pregnancy (e.g., preeclampsia) are particularly sensitive to these upper-airway changes [21]. As pregnancy advances, the uterus compresses the bladder and restricts the diaphragm, further restricting breathing [22]. The enlarged uterus also makes for difficulties in turning or movement during sleep, resulting in night awakenings, the most common sleep disturbance in pregnancy [1, 5]. As labor approaches, the secretion of oxytocin, the hormone responsible for uterine contractions but which also promotes wakefulness, increases and peaks at night, resulting in sleep fragmentation and potentially insomnia [23]. Symptoms of several sleep disorders, including OSA, RLS, and insomnia, are all at their most severe in the final trimester [24, 25].

Self-report data confirm that the significant physical, hormonal, and psychological challenges of pregnancy leave women at heighted risk for insufficient and/or poor-quality sleep during these periods. For example, a Finnish study of 1646 women found that 23.4% were sleeping <7 h per night, and the majority (82.6%) reported a worsening of their sleep quality from pre-pregnancy [2]. An Internet survey of 2427 pregnant women found that, regardless of trimester, women experienced poor sleep quality (76%), insufficient nighttime sleep, and significantly disrupted sleep (e.g., 33.1% early insomnia). Total sleep duration decreased across pregnancy from 7.61 to 6.85 h on average per night, and increased number and duration of night awakenings were reported as the pregnancy progressed [1]. A recent meta-analysis revealed 45.7% of 11,002 pregnant participants reported poor sleep quality at some point during pregnancy and that sleep quality significantly decreased from the second to third trimester [26].

Self-report measures of sleep quality and quantity during pregnancy do not necessarily reflect objectively measured sleep (e.g., [27, 28]). One method of objective sleep assessment is polysomnography (PSG), a labor-intensive procedure that requires participants to sleep in a laboratory. This makes recruitment of pregnant and postpartum women for these studies a challenge. What work has been done reveals inconsistent findings and the need for more research into the sleep architecture of pregnant and postpartum women [29–31]. However, some similarities in the objectively measured sleep of pregnant women have been found, including a decrease in stage 4 sleep (now combined with stage 3 and referred to as stage N3) in the first and third trimesters, as well as a decrease in total rapid eye movement (REM) sleep. Women in the third trimester also have poorer sleep efficiency (percentage of time spent asleep vs. time in bed) and increased awakenings after sleep onset compared with controls [32, 33].

21.1.2 Sleep in the Postpartum (Delivery to 1 Year Postpartum)

Given the rapid fall in estrogen and progesterone levels post-delivery [34], edema, and the disordered breathing that it causes, usually improves quickly after birth, aided by gestational weight loss in the first 2–6 weeks postpartum [35, 36]. This often results in the rapid resolution (~1 month postpartum) of the more prevalent gestational sleep disorders, OSA and RLS [14, 25, 37]. However, some studies suggest the postpartum comes with circadian phase shifts [38] and disruptions in nocturnal melatonin patterns [39], both of which may contribute to poor postpartum sleep quality and a heightened risk of sleep disorder development. While the pain of pregnancy is now resolved, recovery from labor and delivery may impinge on sleep in the postpartum, as can pain and soreness from breastfeeding. Nocturnal infant caregiving interferes significantly with maternal sleep efficiency [40, 41]. Total maternal sleep time and sleep efficiency increase gradually as the infant's circadian rhythm matures, with a transition from interrupted to uninterrupted sleep usually occurring at approximately the 12th postpartum week [40, 42]. This parallels the resolution of complaints of insomnia by some women around the same time [43].

21.2 Sleep Disorders in the Perinatal Period and Their Treatment

Despite the well-documented reluctance on the part of pregnant and breastfeeding women to take medications (e.g., [44–47]), a recent study of 2427 pregnant women found that 1 in every 25 reported sleep-related medication use at minimum of three times per week, while more than one in ten reported use in the past month [1]. Unfortunately, there is a dearth of high-level outcome data on pharmacotherapy for the majority of sleep disorders during the perinatal period since pregnant and

breastfeeding women are systematically excluded from drug trials. This highlights the need to approach treatment decisions in a thoughtful, individualized manner, balancing the risks of pharmacologic treatment during pregnancy and lactation to mother and child with the benefit of symptom relief and the risks of an untreated sleep disorder.

21.2.1 Obstructive Sleep Apnea (OSA)

OSA is the most common form of sleep-disordered breathing (SDB) and is characterized by repetitive episodes of upper-airway obstruction resulting in partial or complete airflow cessation, causing oxygen desaturations and arousals from sleep (American Academy of Sleep Medicine [AASM] [48]). Patients may report snoring, witnessed apneas, nocturnal awakenings, nocturia, unrefreshing sleep, and excessive daytime fatigue and sleepiness [37, 49]. The exact prevalence of OSA in pregnancy remains uncertain due to the traditional reliance on self-report measures with poor sensitivity and specificity in terms of diagnosis [50, 51]. Studies using PSG find varying rates; one study of 1509 pregnant subjects found that 15.5% met OSA criteria, for an estimated point prevalence of 4.9% [50]. Another revealed 8.4% prevalence in the first trimester and 19.7% in the third [52], while a study using a wrist-worn device validated against PSG to diagnose OSA identified 37% in the third trimester [53]. The increased incidence of snoring during pregnancy (21–30% [1, 54]), the most common symptom of OSA, would suggest that the prevalence of OSA may well be increased. Risk factors for the development of gestational OSA include increased maternal age and first trimester BMI [52].

OSA, while possibly persisting into the early postpartum period [55], is usually resolved by the second postpartum month [37, 52, 56]. However, recent research suggests persistent OSA is possible [53]; for these women, a repeated PSG is recommended, with severe symptoms requiring continued intervention.

21.2.1.1 Treatment

At present, there are no pregnancy-specific practice guidelines for the treatment of OSA. Recommendations for treatment in the non-pregnant population are generally followed and include continuous positive airway pressure (CPAP) machines and oral devices. However, complementary strategies such as lifestyle modifications (e.g., weight loss) and sleep position training, specifically adjusting the torso elevation to a 45° angularity, have been found to be effective in promoting respiration [57] (please see Table 21.1).

There is no medication that prevents or treats OSA. Modafinil and its R-isomer armodafinil are wake-promoting agents and are sometimes prescribed to patients with OSA to combat symptoms of daytime tiredness [58, 59]. There are no adequate and well-controlled studies of modafinil or armodafinil in pregnant or lactating women, and research shows some teratogenic effects, and breast milk expression, in animal studies [60, 61]. Please see Sect. 21.2.4.1.

Table 21.1 Expert recommendations based on scientific evidence and clinical experience

Sleep disturbance/ disorder	Treatment	Recommendation
OSA	CPAP or oral appliance therapy; positional therapy if applicable.	Treat if apnea is significant or patient is symptomatic; may improve or resolve postpartum.
RLS	Iron supplementation if serum ferritin is low; if symptoms are severe, consider levodopa, carbidopa, BZDRAs, or, in very severe cases, low-dose oxycodone; inform patient of potential adverse effects.	Stress importance of conservative/non-pharmacological measures.
Insomnia	CBT-I; antihistamines; cautious use of BZDRAs, sedating antidepressants, and antipsychotic medications.	Medication should be second-line treatment and seen as short-term treatment; use if CBT-I is not helpful.
Narcolepsy	Data on safety of medications other than antidepressants is too limited; switch to a non-TCA antidepressant if possible for cataplexy; if narcolepsy is severe, patient should be continued as usual treatment while being informed of potential risks and lack of data.	For less severe degrees of narcolepsy, avoid medications if possible; inform patient of potential risks and lack of data regarding safety in pregnancy and breastfeeding.

21.2.2 Restless Legs Syndrome (RLS)

RLS is described as a sensorimotor neurological disorder that causes uncomfortable sensations in the legs, leading to a desire to move the legs to relieve the discomfort. Symptoms often appear or worsen in the evening and/or nighttime and when at rest [15, 48, 62]. RLS is one of the most common sleep disturbances during pregnancy; its prevalence is approximately two to three times higher during pregnancy, affecting 10–34% of pregnant women [14, 63–65]. Hallmark symptoms during pregnancy include leg cramps, positional discomfort, venous stasis, leg edema, and compression or stretch neuropathies [25, 66]. Pregnancy exacerbates primary RLS, and RLS may occur in a new-onset/gestational form [67]. This relationship has been suggested to be due to the relative iron deficiency during pregnancy, although alternative connections have been proposed, for example the influence of hormonal changes [13, 66, 68]. The exact pathophysiology of gestational RLS remains unknown. Risk factors of RLS in pregnancy include OSA, RLS in previous pregnancies, advanced gestational age, snoring in the first trimester, weight gain, and pre-pregnancy depression [6, 68–70]. RLS symptoms usually increase in severity as pregnancy progresses and often resolve with childbirth [14, 25, 63, 65].

21.2.2.1 Treatment

For mild cases of RLS, lifestyle changes (e.g., sleep habits, exercise, decreased caffeine consumption) are usually recommended [25, 66, 67]. Iron supplementation is also recommended, in pregnancy or otherwise, particularly if serum ferritin is

<75 μg/L [25]. For RLS secondary to OSA, CPAP treatment to resolve the primary OSA is necessary [69]. Pharmacotherapy is recommended in moderate to severe cases of RLS (symptoms occurring at least twice per week and causing moderate distress at minimum) and where non-pharmacological approaches have failed [25, 71]. While there is a substantial evidence base for the efficacy and safety of these medications in the general population, no such work has been performed for these treatments during pregnancy and lactation (please see Table 21.1).

Anticonvulsants

Gabapentin enacarbil, gabapentin, and pregabalin are first-line medications for the treatment of chronic non-gestational RLS [25, 66, 71]; gabapentin enacarbil is the only one of the three approved for treatment of RLS in the general population by the US Food and Drug Administration (FDA) [72]. However, consensus clinical practice guidelines as laid out by the International Restless Legs Syndrome Study Group (IRLSSG) ruled all three drugs as having too little safety data to recommend their use during pregnancy [25]. A 2014 review examining pregnancy registries, case reports, and cohort studies of gabapentin-exposed pregnancy reveals no increased risk of major congenital malformations [73]. However, no large-scale rigorous empirical work on gabapentin in pregnancy exists. Embryofetal toxicity is observed in animal studies at less than the maximum recommended human dose [74].

All three medications are expressed in breast milk; however, in the case of gabapentin, only 1–4% of the maternal weight-adjusted dose is estimated to be received by the infant, and no adverse effects have been reported in the epilepsy literature for the neonate [74–78]. Data on gabapentin enacarbil and pregabalin during lactation suggest risk to the neonate in animal studies; they are not recommended for use in the postpartum [25, 74, 76].

Dopamine Agonists

Along with the antiepileptics, dopamine agonists (dopaminergics) are considered first-line pharmacotherapy for RLS in the general population [25, 71, 79]. These include levodopa, pramipexole, rotigotine, bromocriptine, cabergoline, and ropinirole. At present, only ropinirole, pramipexole, and the rotigotine patch are approved for the treatment of RLS by both the FDA and European Medicines Agency; all other medications are considered off-label for the treatment of RLS [80–85]. Consensus guidelines suggest that bromocriptine, cabergoline, and pergolide should not be considered during pregnancy due to the risk of fibrotic cardiac valvulopathy [86, 87]. Pramipexole, ropinirole, and rotigotine are rated as having too limited an evidence base for consensus on use in pregnancy [84, 88, 89]. Levodopa, in combination with the decarboxylase inhibitor carbidopa to ensure adequate blood-brain barrier penetration [90], is the only agonist suggested by the IRLSSG to be considered for the treatment of gestational RLS [25] due to a larger volume of safety data during pregnancy than the other dopamine agonists [91–94]. However, this data is not based on well-controlled studies in pregnant women, and animal studies report teratogenic effects. As such, levodopa plus carbidopa (Rytary) should only be used if the potential benefits justify the potential risk to the fetus [95].

Dopaminergics are inhibitors of prolactin which, in turn, reduces breast milk production [96]. This coupled with a lack of data in lactating mothers and their infants boast too little evidence to recommend these medications during breastfeeding [25, 84, 88, 89].

Benzodiazepine Receptor Agonists (BZRAs)

BZRAs, which include benzodiazepine-related medications and z-drugs (e.g., zolpidem, zopiclone, zaleplon), are a class of psychoactive drugs that result in sedative, anxiolytic, anticonvulsant, and muscle relaxant properties [97]. The effectiveness of these drugs for RLS in the general population is currently unknown [98], and they are not recommended as first-line therapy for RLS in pregnancy or otherwise [25, 99]. However, both the AASM and the IRLSSG consensus guidelines suggest the anticonvulsant benzodiazepine clonazepam can be used as a secondary or adjunctive medication for RLS in the general population [25, 99]. Clonazepam, along with many benzodiazepines, is a hypnotic, which is helpful in RLS in that it reduces sleep latency, prolongs total sleep time, reduces awakening after sleep onset, and diminishes the arousal threshold [100, 101]. It may also reduce sensory RLS symptoms and reduce anxiety, which is commonly associated with RLS [102]. The IRLSSG consensus guidelines suggest clonazepam may be used in pregnancy and while breastfeeding due to the lack of a significant teratogenic risk and no withdrawal/sedation for the newborn [103–106]; however, they do recommend avoiding its use during the first trimester of pregnancy [25]. The American College of Obstetricians and Gynecologists (ACOG) suggests caution when using any benzodiazepine during pregnancy as they may add to the risk of maternal respiratory depression [107]. Please see Chaps. 11 and 12 in this book for detailed information on the safety of benzodiazepines and z-drugs during pregnancy and lactation.

Opioids

Not all RLS patients respond to dopamine agonists and anticonvulsants, and use of these agents has been associated with adverse effects and augmentation (except for gabapentin [108]), where symptoms may worsen, start earlier in the day, and spread to other parts of the body [109]. In refractory RLS, combination treatment should be considered for patients with symptoms that cannot be controlled with a low-dose monotherapy of either treatment class. Where this fails and/or when symptoms are severe, opioids can be considered as monotherapy or add-on treatment [25, 109]. There is data that suggests that opioid receptors are involved in the pathogenesis of RLS [110, 111], and some clinical work suggests opioids can improve or relieve RLS [93, 112–114]. However, high-quality data on the safety of opioid treatment in RLS is lacking in the general population [115], and the literature on opioid use in the pregnant non-RLS patient suggests a risk of birth defects [116, 117], neural tube defects [118], and neonatal abstinence syndrome [119]. Given all this, the consensus treatment guidelines limit their recommendation of opioid treatment during pregnancy to short-term, low-dose oxycodone (5–20 mg/day) in the extremely rare instance of very severe, very refractory RLS during the second or third trimester [25]. Its use during breastfeeding, however, is not recommended, given evidence

suggesting CNS depression and opioid toxicity in the infant [120, 121]. In the case of severe RLS that is unresponsive to other treatments, low-dose tramadol is suggested during lactation, however not for mothers breastfeeding premature or ill infants due to a lack of safety data [25, 122].

21.2.3 Insomnia

Insomnia is defined as one or more of the following: difficulty initiating sleep, difficulty maintaining sleep, and awakening from sleep too early, all with subsequent impaired daytime functioning [48, 62]. Insomnia is highly prevalent in pregnancy, with rates of symptoms of insomnia reported up to 74% [1, 123]. Symptoms of insomnia often become more severe as pregnancy progresses, and there is a 2.03 times higher risk of insomnia in the final trimester of pregnancy [124]. Cortical hyperarousal and chronic sleep deprivation contribute to the onset of insomnia; however, insomnia may either be a symptom or a disorder [125]. For the vast majority of those in the perinatal period, insomnia is a symptom of the physical and hormonal disruptions of pregnancy, but mood disorders, breathing-related sleep disorders (including OSA), and RLS [1, 126–128] may also contribute. Such secondary insomnia often resolves with delivery (or treatment of the primary cause). However, nighttime feeding and the frequent nocturnal awakenings among infants contribute to poor sleep quality and quantity during the postpartum. Indeed, unlike in the cases of gestational OSA and RLS, symptoms of insomnia do not resolve in the majority of women after delivery; poor sleep quality and insomnia appear relatively stable from pregnancy to postpartum for many women [26, 129–131].

21.2.3.1 Treatment

The AASM clinical practice treatment guidelines for insomnia [132], the American College of Physicians clinical practice guidelines for the management of insomnia in adults [133], the European Sleep Research Society guidelines for the treatment of insomnia [134], and the Canadian Sleep Society [135] all strongly recommend cognitive behavioral therapy for insomnia (CBT-I) as a first-line treatment for chronic insomnia. Preliminary evidence suggests CBT-I is as effective as sedative hypnotic treatment options in the short term, and superior in the long term, for the general population [136, 137]. Two studies in the perinatal population suggest CBT-I reduces symptoms of insomnia during pregnancy [138] and the postpartum [139]. However, large-scale efficacy trials are needed.

For those patients unable to participate in CBT-I or who still have symptoms despite participation, pharmacotherapy should be considered as monotherapy or as a short-term adjunct to CBT-I [132–134]. However, the American College of Physicians makes no specific recommendations for any one medication, largely due to insufficient or poor-quality long-term evidence for or against any medication and a lack of safety data [133]. The AASM practice treatment guidelines make recommendations for the general population but are all accompanied by a strength rating of "weak" due to insufficient evidence for or against any one medication or a difficult to determine balance of benefits vs. harms [132]. They also do not make any

recommendations or statements for or against the use of any medication in pregnancy or during lactation. Clinicians are therefore encouraged to make treatment decisions based on the context of treatment goals, comorbidities, prior treatment responses, and patient preferences, with consideration for the specific variant of insomnia under consideration (onset, maintenance, and/or early morning insomnia) (please see Table 21.1).

Benzodiazepine Receptor Agonists (BZRAs)

Short-intermediate acting BZRAs have good evidence for the short-term management of insomnia in the general population [132–134]. However, only triazolam and temazepam are recommended for use by the AASM [132] and only temazepam by the Canadian Sleep Society [140]. Moreover, the majority of benzodiazepines carry a risk of side effects, abuse, dependence, and withdrawal, as well as a risk to the fetus [141–146]. As such, the z-drugs are usually prescribed in pregnancy and postpartum and include zolpidem, zaleplon, and eszopiclone [140, 147–149]. These drugs exert their effects via selective targeting of the GABA receptor to produce a sedative effect [150]. Eszopiclone and zolpidem reduce the time to sleep onset and prolong sleep duration, while the extremely short half-life of zaleplon improves sleep onset, but not maintenance [151–153]. While the z-drugs appear to offer a better safety profile over benzodiazepines, they still come with potential adverse side effects such as sedation, anterograde amnesia, and complex sleep-related behaviors [154–156]. All three z-drugs are recommended for treatment of insomnia in the general population by the AASM [132], the European Sleep Research Society, and the Canadian Sleep Society, all of whom specify their recommendation is at the lowest effective dose for short-term use [134, 140].

There are no large-scale rigorously controlled studies of zolpidem, zaleplon, or eszopiclone in pregnancy. A large Swedish population-based medical birth registry found no increased fetal malformation risk for zolpidem and zaleplon [157], while a study of two nationwide population-based datasets from Taiwan shows an elevated odds ratio for adverse pregnancy outcomes with zolpidem use in pregnancy (small for gestational age, low birth weight, preterm delivery), but not congenital malformations [158]. Animal studies suggest no teratogenicity of eszopiclone or zolpidem [159, 160].

Research suggests that low levels of both zaleplon and zolpidem are secreted into breast milk [159, 161]; it is unknown whether eszopiclone is excreted into human breast milk [160]. Effects on the infant are unknown. Please see Chaps. 11 and 12 in this volume for detailed information on the safety of benzodiazepines and z-drugs during pregnancy and lactation.

Melatonin Receptor Agonists

Melatonin is a hormone produced by the pineal gland and is secreted mainly at night in response to regular light/dark conditions. Ramelteon is a selective melatonin receptor (MT_1 and MT_2) agonist and is the first non-BZRA sleep-promoting medication to be approved by the FDA for treatment of insomnia in the general population [162]; however, it has yet to be approved in Europe [134] or Canada [163]. It is

the only FDA-approved sleep-promoting medication that does not have a direct sedating effect but rather enhances sleep through effects on sleep regulatory mechanisms within the suprachiasmatic nucleus [164]. Due to a short half-life, ramelteon appears to be most efficacious in the treatment of sleep onset insomnia (rather than sleep maintenance), with little to no "next morning" handover effects or withdrawal [165–171]. Ramelteon is one of only two FDA-approved medications for insomnia rated as not having significant potential for abuse (the other is doxepin) by the US Drug Enforcement Administration (DEA) [172].

According to the FDA-approved ramelteon medication guide, ramelteon has been associated with an effect on reproductive hormones, such as decreased testosterone levels and increased prolactin levels. It is not known what effect this medication may have on the fetus. It is unknown whether ramelteon is excreted in human breast milk; it is excreted in the breast milk of rats [162].

Melatonin itself is approved as a medication for the treatment of insomnia only for patients over 55 years old in Europe (Neurim [173]). It is not approved in North America but is available as an over-the-counter dietary supplement and is a popular remedy for general sleep problems and insomnia. A 2013 meta-analysis found that melatonin at doses of 0.1–5 mg had a modest effect on sleep latency, total sleep, and sleep quality and had a favorable adverse effect profile in a non-pregnant sample [174]. However, these over-the-counter preparations come in a variety of doses, and there is sparse, conflicting evidence for the efficacy of melatonin [175–177]. It is not recommended by the AASM [132] nor the European Sleep Research Society guidelines [134]. As with ramelteon, very little is known about the effect of melatonin in pregnancy and breastfeeding, and as such it is not recommended for women in the perinatal period [178, 179].

Antidepressants

Doxepin is a sedating tricyclic antidepressant with a high affinity for histamine (H_1) receptors and is the only FDA-approved antidepressant for the treatment of insomnia in the general population [180]. There is some evidence to support the efficacy of doxepin in the treatment of sleep maintenance insomnia, with evidence of no adverse events in excess of placebo [167, 169, 181–184]. There is no evidence that doxepin carries any risk of tolerance or abuse, and as such it is one of the only two FDA-approved medications for insomnia (the other is ramelteon) that have not been designated by the DEA as having a significant potential for abuse [172]. Doxepin is recommended by the AASM at a low dose [132].

Very little research exists on doxepin in pregnancy or breastfeeding. Animal studies reveal developmental toxicities and decreased fetal survival [180]. Reports of detectable serum levels in breastfed infants of mothers on doxepin exist, as do two case reports of adverse effects in infants [185–187].

Trazodone is a sedating antidepressant commonly prescribed as a hypnotic at low doses [188], off-label. Evidence for the efficacy of trazodone is very weak [189] and sparse [132], and it is not recommended by the AASM in the general population [132]. There are no adequate and well-controlled studies of trazodone in pregnant or lactating women. Animal studies reveal congenital anomalies and fetal

reabsorption; trazodone and/or its metabolites have been found in the milk of lactating rats [190].

The use of antidepressants to treat comorbid depression may alleviate both insomnia and depressive symptoms [191, 192]. Please see Chaps. 5 and 6 in this volume for detailed information on the use and safety of antidepressants during pregnancy and lactation.

Orexin Receptor Antagonists

Orexin receptor antagonists are a relatively new type of insomnia medication. These medications exert their therapeutic effect via antagonism of orexin receptors, whose neurotransmitters play a role in wakefulness and sleep [193–195]. Suvorexant is the only orexin receptor antagonist approved by the FDA for the treatment of insomnia characterized by difficulty with sleep onset and/or sleep maintenance [196] and is recommended for the treatment of sleep maintenance insomnia in the general population by the AASM [132]; it has yet to be approved in Europe [134] or Canada [197]. There are no adequate and well-controlled studies of suvorexant in pregnant or lactating women. Decreases in fetal body weight and toxicity have been found in animal studies [198]. It is unknown whether suvorexant or its metabolites are excreted into human milk; they are excreted in rat milk at levels higher than in maternal plasma, and effects on the nursing infant are unknown [198].

Antipsychotics

Antipsychotics, particularly quetiapine and olanzapine, are commonly prescribed for sleep disorders, despite not being approved in Canada or the United States for such an indication [199, 200]. These drugs are antagonistic to the serotonin (5-HT2) and histamine (H1) neurotransmitter systems, resulting in sedation [201]. While recent work suggests the safety of antipsychotics in pregnancy [202–205], both quetiapine and olanzapine are excreted in breast milk, and there is insufficient evidence to recommend their use during breastfeeding [206–208]. Moreover, there is a paucity of evidence on the efficacy and risks of the use of antipsychotic medications for insomnia in the general population [209]. The European guidelines recommend against these medications [134], and a 2008 AASM clinical guideline paper on the evaluation and management of insomnia suggests they may only be suitable for those who may benefit from the primary action of these drugs as well as from the sedation [179]. Please see Chaps. 7 and 8 in this volume for detailed information on the use and safety of antipsychotics during pregnancy and lactation.

Anticonvulsants

Antiepileptic medications (gabapentin and tiagabine) are sometimes prescribed for insomnia in the general population due to their sedative effects, off-label. Gabapentin decreases the activity of wake-promoting glutamate and norepinephrine systems, and tiagabine enhances sleep by inhibiting the reuptake of GABA [172, 210]. Some evidence for gabapentin's ability to increase total sleep time, but not sleep onset, exists [211, 212], and tiagabine has been found to increase slow-wave sleep but has

not been shown to improve sleep onset or sleep maintenance consistently [172]. Tiagabine is explicitly not recommended for use in the general insomnia population by the AASM [132]; a recommendation for gabapentin is not provided due to a scarcity of research. Similarly, the European guidelines do not include anticonvulsants in their recommendations due to lack of data [134].

There is very little information on the use of tiagabine in pregnancy. FDA data reveal teratogenic effects in animal studies [213]. It is not known whether tiagabine is excreted in breast milk [213, 214]. Please refer to Sect. 21.2.2.1 "Anticonvulsants" for a discussion of gabapentin during pregnancy and lactation.

Antihistamines

Antihistamines are one of the most commonly used medications in the pregnancy period because of their wide availability as over-the-counter medication and use to combat nausea and vomiting [215, 216]. The H_1 receptor antagonists, known as the first-generation antihistamines, are well recognized for their sedating effects for which they are often used. Only diphenhydramine (Benadryl) and doxylamine (Unisom) have been approved by the FDA for the treatment of insomnia [217, 218]. However, the AASM and the European Sleep Research Society do not recommend the use of any antihistamine, and diphenhydramine in particular, for the treatment of insomnia in the general population due to insufficient evidence for their efficacy [132, 134].

A recent systematic review and meta-analysis reveals that use of these antihistamines in the first trimester is not associated with an increased overall risk of major fetal malformations or other adverse pregnancy other outcomes (e.g., spontaneous abortions, low birth weight, prematurity, stillbirth) [215]. However, the ACOG suggests caution when using antihistamines during pregnancy as they may add to the risk of maternal respiratory depression [107].

Very little empirical work on either doxylamine or diphenhydramine in breastfeeding exists. However, the ACOG and the Motherisk Program, the Canadian teratogen information service on the risk and safety of medications during pregnancy and breastfeeding, suggest that antihistamines in general are not contraindicated during breastfeeding [219–221].

21.2.4 Narcolepsy

Narcolepsy can be a highly disabling chronic neurological disorder that affects approximately 1 in every 2–3000 people [125, 222, 223]. Diagnostic criteria include daytime periods of an irrepressible need to sleep and/or lapsing into sleep and one or more of the following: episodes of cataplexy—sudden loss of muscle tone when awake, triggered by strong emotions—cerebrospinal fluid hypocretin-1 deficiency, and/or abnormal REM sleep [62, 224, 225]. Approximately 60–70% of patients with narcolepsy suffer from episodes of cataplexy [223, 226–229], a characteristic that distinguishes narcolepsy type 1 (with cataplexy) from narcolepsy type 2 (without cataplexy) [48]. Core symptoms for both types include excessive daytime

sleepiness, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep [223, 229]. The age of onset for narcolepsy usually encompasses the childbearing years [224, 230]. Narcolepsy persists throughout pregnancy, but research on how pregnancy affects the course of narcolepsy and vice versa is sparse [224, 231]. Managing sleep disturbance during the perinatal period is a struggle for most healthy women. Women with narcolepsy must cope with the added sleep disruptions and excessive sleepiness endemic to the disorder, as well as make the difficult decision between the costs of pharmacotherapy versus untreated narcolepsy during pregnancy and the postpartum period.

21.2.4.1 Treatment

Narcolepsy patients often require daily medication to control excessive sleepiness and cataplexy. These medications either target sleepiness or cataplexy, but not usually both. As such, co-administration of two or more classes of medications may be needed in some patients to adequately address symptoms. The most up-to-date guidelines for the treatment of narcolepsy from the AASM suggest pharmacotherapy should focus on (1) excessive daytime sleepiness; (2) sleep disruption; and (3) cataplexy, hypnagogic hallucination, and sleep paralysis [232]. Unfortunately, many of the medications that target these symptoms lack published data regarding their effect on the developing fetus or neonate. An international survey of sleep clinicians showed that the majority of physicians caring for women with narcolepsy advise their patients to discontinue medications during conception, pregnancy, and breastfeeding [225]. In patients with less severe presentations of the disorder, this caution is unlikely to be misplaced. However, patients with a history of complete collapse related to cataplexy may place themselves as well as their child at risk if left untreated. The risks of untreated cataplexy in an individual perinatal patient need to be weighed against the risks associated with any individual medication (please see Table 21.1).

Modafinil and Armodafinil

Modafinil and armodafinil are recommended as first-line pharmacotherapy treatment for the excessive daytime sleepiness of narcolepsy in the general population by the AASM [232] and are approved by the European Medicines Agency [233] and the FDA for the excessive daytime sleepiness caused by both narcolepsy and OSA [60, 234, 235]; modafinil is approved by Health Canada for this indication [236]. They are two of the most oft prescribed medications for the excessive daytime sleepiness caused by narcolepsy [237], although armodafinil's longer half-life and ease of dosing often make it preferable over modafinil [238, 239]. Both are efficacious [232, 240], with low abuse potential and a favorable side effect profile [241, 242]. However, these medications are less efficacious than amphetamine or methylphenidate and are ineffective for cataplexy [241–243].

Data on the use of these compounds in pregnancy are limited to case reports and survey studies that suggest safety in pregnancy [224, 225, 244]. However, the product monographs for both compounds indicate that intrauterine growth restriction and spontaneous abortion have been reported in association with armodafinil and

modafinil. There are no adequate and well-controlled studies of either drug in pregnant or breastfeeding women, and the European Medicines Agency and the FDA caution against the use of these medications during pregnancy and lactation [60, 61, 245]. Animal research shows some developmental toxicity and breast milk expression; it is not known if either drug is excreted in human breast milk [60, 61].

Sodium Oxybate

Sodium oxybate is considered the gold standard of treatment for cataplexy in the general population [230] and is approved for this indication in Canada [246], Australia [247], and Europe [245]. It is the only drug approved by the FDA for the treatment of both daytime sleepiness and cataplexy [248]. The 2011 guidelines from the European Academy of Neurology [245] recommend sodium oxybate as first-line therapy for cataplexy, as does the AASM [232]. The AASM also recommends it as effective for treatment of daytime sleepiness and disrupted sleep due to narcolepsy and possibly for the treatment of hypnagogic hallucinations and sleep paralysis [232]. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous inhibitory neurotransmitter. Sodium oxybate has been found to result in a significant reduction in cataplexy attacks and excessive daytime sleepiness and is well tolerated [238, 239, 249–254]. However, there is abuse potential with this medication [255]. Also, it has a very short half-life, making treatment adherence difficult [256]. Of note are reports of this medication worsening sleep-disordered breathing and causing central apneas [257, 258], so caution is warranted.

Research on sodium oxybate in human pregnancy is lacking and as such is not recommended during pregnancy by the European Medicines Agency [259] or the European Academy of Neurology [245]. Animal studies show no developmental toxicity, although an increased rate of stillbirths has been found [260]. This compound is excreted in human milk, and the FDA cautions that there is insufficient information on the risk to a breastfed infant [260]. However, there are several recent case reports of sodium oxybate use in breastfeeding women that suggest no risk to the infant if an interval of 4–5 h between sodium oxybate ingestion and nursing is observed [230, 261, 262].

Central Nervous System Stimulants

In the case of disabling daytime sleepiness that does not respond to modafinil or armodafinil, and where sodium oxybate is not recommended or required, the AASM recommends methylphenidate (Ritalin) and the amphetamines (e.g., methamphetamine, dextroamphetamine) as second-line agents for the treatment of excessive daytime sleepiness due to narcolepsy in the general population [232], while the European Federation of Neurological Societies only recommends methylphenidate [245]. These are FDA approved for use in narcolepsy [263]. In Europe only methylphenidate is approved for narcolepsy [245, 264]. Methylphenidate is often preferred to the amphetamines due to a slightly improved safety profile [265]. These drugs work by causing an increase in the release of noradrenaline, dopamine, and serotonin, and inhibition of reuptake of amines by dopamine transporter, resulting in promotion of wakefulness [241]. All these medications, methamphetamine in

particular, have a high potential for abuse and side effects [242, 251, 266], although some research suggests a low risk of addiction among patients with narcolepsy [267, 268].

There is very little research on methylphenidate in pregnancy and breastfeeding, and much of what has been done examines amphetamine-addicted mothers or those with ADHD. The sum of the work on methylphenidate suggests this compound is not a human teratogen [265, 269, 270]. However, there are reports that show that methylphenidate increases rates of spontaneous abortions, prematurity, small for gestational age [271, 272], cardiac malformations [204], and perinatal complications [273]. Methodological limitations plague many of these studies, and results are often conflicting (e.g., [274, 275]). Methylphenidate has been detected in small amounts in breast milk but is generally undetected in the infant's blood [276, 277].

Research to date suggests amphetamines do not pose a risk of fetal malformations [274, 278]. A recent review of the impact of the use of amphetamines in the treatment of attention deficit hyperactivity disorder (ADHD) during pregnancy and lactation showed a reduction in birth weight and increased rate of prematurity, maternal hypertension, and postpartum hemorrhage [274]. Methamphetamine use in particular is associated with an increase in the rate of central nervous stress in the newborn [279], younger gestational age and lower birth weight [280–282], growth restriction [274], and increased anxiety/depression, emotional reactivity [279], increased externalizing behaviors, and ADHD symptoms in the child [283]. However, the difficulty with this data is that it is derived largely from case reports and studies of women addicted to amphetamines and/or other psychotropic drugs or mothers with ADHD. Hence, these important confounders should be considered in the evaluation of this data.

Amphetamines are excreted in human milk at relatively high levels [265, 284–286]; very little is known about the short- or long-term consequences on the nursing infant. The European Academy of Neurology recommends avoiding these medications in the perinatal period [245].

Antidepressants (SSRIs, SNRIs, MAOIs, and TCAs)

Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) are recommended for cataplexy and to a lesser extent for hypnagogic hallucinations and sleep paralysis by both the AASM [232] and the European Federation of Neurological Societies [245], off-label. Monoamine oxidase inhibitors (MAOIs) are recommended for excessive daytime sleepiness. The evidence base for these compounds in narcolepsy is limited. The European guidelines identify TCAs as the most effective of the alternatives to sodium oxybate for cataplexy [245], such as imipramine, protryptiline, and particularly clomipramine [242, 245, 287]. These medications are effective at low doses, but their anticholinergic properties result in certain side effects (e.g., sweating, sexual dysfunction) [288]. The SNRI venlafaxine is widely recommended and used for cataplexy, but clinical evidence of efficacy is lacking [241, 245, 287–290]. SSRIs such as fluoxetine and fluvoxamine are used and recommended for cataplexy, although there are no clinical trials of efficacy and high doses are often needed for

therapeutic effect [242, 287, 291, 292]. Selegiline (MAOI), a precursor of amphetamine [293], is used in Europe as an option for excessive daytime sleepiness and cataplexy [232, 245], although the need for high doses and interactions with certain foods and drugs do not make it an ideal treatment [294]. It should be noted that increases in cataplexy frequency and severity have been seen in abrupt discontinuation of antidepressants [295–297]. Moreover, there is some data that suggests both mirtazapine and venlafaxine are associated with higher rates of restless legs syndrome and periodic limb movements, but this data is not conclusive [298].

Very little data on these drugs during pregnancy and breastfeeding in women with narcolepsy exists. Research on these drugs in other populations suggests no risk of teratogenicity or other significant risks to the fetus or infant (e.g., [299–303]). However, additional work with more rigorous study designs is needed, particularly on women with narcolepsy. The use of antidepressants to treat comorbid depression may be recommended given that narcolepsy is associated with a high prevalence of self-reported depressive symptoms [304, 305]. Please see Chaps. 5 and 6 in this volume for detailed information on the use and safety of antidepressants during pregnancy and lactation.

Pitolisant

There are several new medications in development for the treatment for narcolepsy. One of the most promising is the stimulant pitolisant, a histamine H3 receptor (H3R) antagonist/inverse agonist. Pitolisant has been recently approved for the treatment of narcolepsy with or without cataplexy in Europe [306]. Clinical trials conducted on pitolisant reveal its efficacy for excessive daytime sleepiness [307] as well as cataplexy [308]. The safety profile of pitolisant appears dose related and easily managed; however, the sample sizes in the clinical trials were small, and more studies are needed to assess safety and long-term efficacy [306]. There are no systematic data on pitolisant in pregnancy or breastfeeding; animal studies show pitolisant and its metabolites cross the placenta and are excreted in breast milk [306, 309]. The European Medicines Agency does not recommend its use during the perinatal period [309, 310].

21.3 Risks of Untreated Sleep Disturbances During Pegnancy and the Postpartum Period

Failure to treat sleep disorders during the perinatal period can result not only in the worsening of the respective disorder but obstetric complications and poor maternal and fetal/infant outcomes. Some of these outcomes vary by sleep disorder, while others cut across sleep disorder type. Disturbed sleep is a hallmark of many sleep disorders, and failure to treat it comes with its own set of risks. These will be discussed in Sect. 21.3.3. “Insomnia” below but apply to each of the disorders discussed in this chapter.

21.3.1 Risks of Untreated OSA

There is a literature examining the association between OSA and significant morbidity and mortality in obstetrical patients, mostly with conflicting or inconclusive results. This is largely due to small sample sizes, variability in how sleep-disordered breathing is assessed, and lack of control of major confounders such as smoking and obesity [311, 312]. However, a recent well-controlled, large prospective cohort study found elevated risks for preeclampsia, hypertensive disorders, and gestational diabetes in those with objectively assessed OSA, with an increasing exposure-response relationship between apnea-hypopnea index or apnea severity and hypertensive disorders and gestational diabetes [313]. This work confirms previous cross-sectional and retrospective studies looking at OSA and the risk of hypertensive disorders and gestational diabetes during pregnancy (e.g., [55, 314–316]), as well as a recent large population-based cohort study that found a significant association between OSA and gestational diabetes and hypertension [317]. This study also found a significant association between OSA and preeclampsia, eclampsia, cardiomyopathy, congestive heart failure, and hysterectomy. A large, retrospective cohort study found a heightened risk of preterm birth for women with OSA [318]. This research did not assess the status and/or compliance with treatment in their OSA samples. Systematic investigations have not been published on the effect of treatment of gestational OSA on pregnancy outcomes; as such, it is unknown whether treatment of sleep-disordered breathing in pregnancy would reduce the risks of these adverse outcomes.

21.3.2 Risks of Untreated RLS

Research on the relationship between RLS and complications related to pregnancy and labor is, at present, inconclusive. Some work shows an association between symptoms of RLS and preeclampsia [319, 320] and cesarean section [321]. A cross-sectional self-report study found an association between severity of symptoms of RLS and gestational hypertension, low neonatal birth weight, and younger gestational age at birth [319]. However, other research found no connection between RLS and gestational age at delivery, cesarean section delivery, birth weight, and 1- and 5-min Apgar scores [322, 323]. Preliminary work shows an increased risk for both antenatal and postpartum depression for those with RLS during pregnancy [70, 324]. While this connection needs to be explored further, it is possible that the overall burden of the disease, and its exacerbation during pregnancy, may render women more susceptible to depression. Also plausible is the chronic insomnia that often accompanies RLS worsens in pregnancy as RLS symptoms increase, leading to depressive symptomatology [319, 323, 324]. These issues are particularly important during pregnancy and must be considered when weighting treatment options.

21.3.3 Risks of Untreated Insomnia

Sleep loss during pregnancy is a risk factor for a host of adverse maternal outcomes, such as gestational diabetes [313, 325], longer labor, cesarean deliveries [323, 326–328], and perception of greater pain during delivery [329]. Adverse neonatal outcomes include preterm birth [318, 330, 331], low birth weight [330], and placental abruption [332]. In the postpartum, maternal neurobehavioral performance declines due to the accumulation of sleep deprivation or fragmentation [333], and negative maternal perceptions of the mother-infant relationship are correlated with disturbed maternal sleep [334]. A longitudinal population-based study found that both intermediate and high levels of chronic insomnia from pregnancy to postpartum were associated with onset of bodily pain symptoms in the postpartum [130].

The relationship between symptoms of insomnia during both pregnancy and the postpartum and the development of depressive symptomatology and/or antenatal and postpartum depression has been well-researched (e.g., [192, 331, 335–342]). Perinatal depression comes with its own set of adverse outcomes, including premature birth, low birth weight, and disorganized sleep in the neonate [343], poor maternal-fetal attachment [344, 345], and later emotional, behavioral, cognitive, and interpersonal problems in the child [345–347]. Long-term effects of postpartum depression on the child can also include an elevated risk of impaired cognitions and decreased academic performance [345]. Perinatal depression is associated with a significantly increased risk for suicide and is among the leading causes for maternal mortality in the postpartum period [348, 349].

21.3.4 Risks of Untreated Narcolepsy

Data on the impact of untreated narcolepsy in pregnancy and postpartum are lacking and are largely restricted to case reports. A small retrospective cohort study in 2010 found no significant differences in occurrence of obstetrical complications or neonatal outcomes between those with pre-pregnancy onset of narcolepsy and post-pregnancy onset, although a higher overall number of pregnancy complications were found for those with pre-pregnancy onset [350]. The same group conducted a larger retrospective self-report cohort study 3 years later and found that mothers with narcolepsy during pregnancy reported anemia and glucose intolerance more frequently than mothers without, as well as an increased rate of cesarean deliveries despite a low incidence of cataplexy during delivery [224]. Neonatal care was affected adversely by symptoms of narcolepsy for 60.1% of those with narcolepsy during pregnancy, a finding replicated by a retrospective case-control study of 25 mothers diagnosed with type 1 narcolepsy, particularly due to fear of a cataplectic attack while feeding or managing their babies [231]. This study found a higher prevalence of gestational diabetes in women with narcolepsy with cataplexy compared to healthy women, but no differences in cesarean sections or complications during delivery. In each of these studies, some participants received pharmacological and/or psychological treatment, while others did not.

More data on the risks of untreated narcolepsy during the perinatal period is needed. Implications of untreated disease include potentially damaging or fatal outcomes of unpredictable sleep attacks and cataplexy for both mother and fetus/infant, such as car accidents. Maternal stress over managing these uncontrollable aspects of narcolepsy is compounded by concern over the impact on the fetus/infant. Treatment decisions must weigh the costs of these potential concerns and stressors over the potential risks of pharmacotherapy.

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