Psychotropic Drugs in Pregnancy and Breastfeeding

16

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16.1 Introduction: Using Psychotropic Drugs in the Perinatal Period

16.1.1 The Risk Associated with Untreated Mental Illness

The perinatal period, including preconception, pregnancy and postpartum, is considered a high-risk time for women suffering of severe and persistent mental illnesses (SPMI). Several international guidelines, mental health organizations and well-known scientific societies recommended implementing proper screening strategies to early and adequately identify, during the perinatal period, vulnerable women affected by or more prone to develop SPMI and providing timely and evidence-based effective therapeutic interventions, including the prescription of psychotropic drugs (PDs) [1–3]. In fact, it has been well documented that maternal mental illness may be associated with adverse perinatal outcomes, including spontaneous abortion, newborns small for gestational age, low birth weight, foetal distress, preterm delivery, neonatal hypoglycaemia, adverse neurodevelopmental outcomes and changes in the foetus-mother attachment [4]. Pregnant women with untreated mental illness are also more likely to be engaged in high-risk behaviours and unhealthy lifestyles, such as smoking, alcohol drinking and drug abuse and inadequate nutrition and folic acid support. Furthermore, in the perinatal period, the risk of suicide and suicide attempts is not uncommon, since the prevalence rate is

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estimated from 5% to 20% of women [5, 6]. Therefore, a careful assessment and treatment of perinatal mental disorders in clinical settings is essential to ensure better maternal, gestational, obstetrician and foetal outcomes.

16.1.2 The Prescription of Psychotropic Drugs: A Risk-Benefit Approach

Prescribing PD during the perinatal period should be reserved only to women suffering from SPMI or in those clinical cases where non-pharmacological strategies have not been effective. Most available data about the safety of PD in the perinatal period come from longitudinal or retrospective observational studies, national birth registries, systematic reviews and meta-analyses. As *controlled randomized clinical trials* (RCT) are not allowed in pregnancy for ethical and medicolegal issues concerning the foetus/neonatal safety, Wisner [7] properly labelled the pregnant women as "the last therapeutic orphans", and the *perinatal psychiatry* is a relevant topic that should be more deeply investigated.

Overall, considering the literature on the safety of PD during pregnancy and breastfeeding, one could argue how there are several studies published on the same topic, which could report really contrasting and different findings, also in terms of relative risk (RR) and statistical significance. The main reason of such discrepancies could be explained considering the different experimental designs and methodological strategies adopted, as well as the existence of relevant "confounding factors", not adequately controlled when the authors analyse the collected data (e.g. the type and level of severity/intensity of maternal psychopathology, comorbid medical conditions, the use/abuse of alcohol, drugs, nicotine, caffeine, etc.). For this reason, clinicians and mental health professionals working in the field of perinatal psychiatry should own a basic knowledge of medical statistics and clinical epidemiology for a better understanding and interpretation of the findings so far published. For example, an increasing RR for a specific major malformation (MM) needs to be evaluated always along with data of its absolute risk (AR), to allow a better assessment of its clinical and epidemiological relevance. If a study, carried out on newborns exposed to sertraline during early pregnancy, reports a "statistically significant risk" of anal atresia (RR = 4.2), clinician should firstly consider the prevalence of anal atresia in unexposed newborns (0.06%) and then calculates the AR in newborns exposed to sertraline which would be very low (AR = 0.25%). This means that about 99% of newborns exposed to sertraline will not be affected by such malformation [8–10].

Several guidelines and consensus guidance by psychopharmacological societies (e.g. British Association of Psychiatry, BAP) have been produced to provide recommendations for the management of PD usage during the perinatal period [11, 12]. In addition, the development of the *teratogen information service* improved the access of pregnant women and their healthcare providers to data concerning the safety and tolerability of PD use during the perinatal period [13]. However, despite reassuring clinical findings on the safety of most PD during the perinatal time, clinicians are

still fearful to prescribe such medications in pregnancy and/or when a mother wishes to breastfeed her own baby. When PDs need to be prescribed during the first 3 months of pregnancy, this kind of "psychopharmacoteratophobia" among clinicians becomes particularly relevant, due to the risk of inducing birth defects or perinatal complications (PC) [14]. Whilst during the late pregnancy, there is also concern for the risk associated with gestational and neonatal adverse events. Moreover, the uncertainness and worries related to the long-term impact on the infant's behavioural, physical and cognitive neurodevelopment following foetal exposure to PDs, together with the clinicians' poor knowledge about the safety and tolerability of PD in pregnancy and breastfeeding, may negatively influence clinician's prescription choices. However, in the last decade, in some European and Northern American countries, there was a significant increase in PD prescription during pregnancy, mainly antidepressants (ADs) and anxiolytics (AX) [15, 16].

Overall, the management of psychopathological conditions in the perinatal period may indeed represent a challenge for mental health professionals, particularly in those conditions in which the pregnancy is unplanned and the pregnant woman is already affected by a SPMI and is currently taking PDs. In the last case, clinicians should be aware that discontinuing a PD could significantly induce a maternal illness relapse. Therefore, clinicians should properly inform the woman and her partner about the risks and the benefits of a PD therapy in the perinatal period and incentive an adequate and timely planning of conception, pregnancy and pospartum management [17].

16.1.3 Aims of the Review

In the present chapter, we briefly summarized all relevant literature focusing on the safety of the most prescribed PDs during the perinatal period. Original cohort studies, systematic reviews and meta-analyses represent the main sources of data here summarized and discussed. More detailed information on the drug epidemiology, clinical pharmacology and safety of PDs in pregnancy and breastfeeding have been recently published by Uguz and Orsolini (Eds.) in *Perinatal Psychopharmacology* [18].

16.2 Antidepressant Drugs in Pregnancy

ADs, currently prescribed in clinical practice, are considered effective in several psychopathological conditions, such as major depressive disorder (MDD), general anxiety disorder (GAD), panic disorder (PD) and obsessive-compulsive disorder (OCD). Among ADs, *selective serotonin reuptake inhibitors* (SSRIs) are nowadays the most frequently prescribed medications in the perinatal period [19, 20]. Moreover, SSRIs have been also the best investigated class of ADs, as far as the safety in pregnancy and breastfeeding is concerned [11, 12].

MDD, often in comorbidity with anxiety disorders, are quite common in the perinatal period, with prevalence rates ranging between 10% and 20%. It is also

estimated that about 20% of women in childbearing age is affected by depression and up to 15% of them may experience clinically significant depressive symptoms during pregnancy and postpartum [2, 13]. Given the high prevalence of depression and/or anxiety during the perinatal period, prescribing ADs is quite common, but with substantial differences across countries, being documented in about 8% of pregnancies, whilst about 3% of women decide to maintain PD treatment throughout all pregnancy [21, 22]. Moreover, pregnant women who discontinued SSRIs appear to be more likely to experience an illness relapse compared to those women who decide to maintain the treatment during their pregnancy (respectively, 68% versus 26%). Around 50% of pregnant women seem to experience a depressive relapse mainly in the first 10 weeks of gestation [23]. According to recent guidelines and expert opinions, prescribing SSRIs to pregnant women suffering from severe depressive episodes and anxiety disorders should be considered a first-line option [12, 24].

16.2.1 Risk of Major Malformations

Overall, data on the risk of congenital MMs in newborns of women treated with AD in their first trimester of pregnancy are relatively reassuring. The majority of the original investigations, systematic reviews and meta-analytic studies documented that the early antenatal use of such medications, particularly SSRIs and venlafaxine, is not associated with an increased risk of MMs, as the prevalence rate reported in such studies is within the rate observed in newborns of the general population, which is estimated between 2% and 5% [25]. Although some studies have found a small increase in RR for cardiac defects (mainly septal anomalies) in newborns in utero exposed to some ADs, particularly with paroxetine [26, 27], many other studies have not recently confirmed such risk [28–31]. In a study including about 950,000 pregnant women, 6.8% were prescribed an AD during the first trimester. The risk of any cardiac defect in infants exposed to SSRIs, in the preliminary analysis, was relatively small but statistically significant (RR = 1.25). However, after controlling for maternal depression and other confounding factors (i.e. adjusted analysis), no significant increase in RR was observed for cardiac malformations between infants of women who took AD and the control group. Furthermore, in this study no significant increase in the risk of cardiac defects was observed with other ADs (e.g. venlafaxine, bupropion) [32]. This study confirmed how accounting for "confounding factors" is of paramount importance when assessing reproductive outcomes such the birth defects, as this risk can be likely associated more to the underlying maternal disorders, particularly if severe, than simply to the medication exposure [32]. These findings were also confirmed in cohort study in which 5154 and 2776 women were prescribed SSRIs, respectively, before and during pregnancy and 200,213 who did not receive SSRIs during pregnancy: no significant difference in cardiac anomalies was reported in children born to women exposed to prescribing ADs. However, it was found an increased risk of specific cardiac defects in newborns of older women and in those with type 2 diabetes, body mass index (BMI)

above 30 kg/m^2 and with a history of alcohol and/or illicit drug use, independently by AD prescriptions [33].

Overall, reassuring data concerning single SSRI agents have been also reported, even though few studies found a small increased risk of birth defects for some drugs (e.g. paroxetine and fluoxetine), even though without a specific pattern of MMs. However, most of these studies suffer from several methodological flaws and should be interpreted with caution, as in other investigations and critical review, this association was not observed or strongly questioned [34, 35]. Among the class of serotonin noradrenaline reuptake inhibitors (SNRIs), data on the *venlafaxine* and *duloxetine* are rather reassuring, as no risk of birth defects was found in the studies so far published, even though the amount of data concerning these ADs are lesser than those published for SSRIs [36–38]. No information is available on *vortioxetine*. Studies on the foetal safety of other ADs (e.g. tricyclics, mianserin, trazodone, mirtazapine and agomelatine) are lacking, because these drugs have been less frequently prescribed in the perinatal period; therefore, their use should be not recommended in the early pregnancy and during the breastfeeding.

16.2.2 Risk of Adverse Gestational and Neonatal Outcomes

16.2.2.1 Preterm Birth, Spontaneous Abortion and Low Birth Weight

Studies assessing the risk of *preterm birth*, in women exposed to AD during gestation, reported conflicting results [39]. The first investigation was a prospective observational study in which 238 pregnant women were categorized into three mutually exclusive exposure groups: (a) with depression and treated with SSRIs; (b) with depression but untreated; and (c) with no depression and no SSRI treatment. Women with depression treated with SSRIs and those with depression but untreated had higher rates of preterm birth (23% and 21%, respectively), as compared to control group reporting 6% of preterm birth [40]. Different findings have been reported in a study on the risk of SSRIs and perinatal outcomes, including preterm birth. The sampling included 845,345 offspring. All pregnancies included in the analysis were classified as (a) exposed to SSRIs (15,729); (b) unexposed to SSRIs but with a psychiatric diagnosis (9652); and (c) unexposed to drugs and without a psychiatric diagnosis (31,394). SSRI treatment was associated with a significantly lower rate of late and early preterm birth, and caesarean delivery, compared to women affected by psychiatric disorders who were not taking SSRIs. The authors suggest that treating a depression with an AD appears "to be protective of preterm birth" [41].

Therefore, available data are not enough to establish if there is a causal association between exposure to ADs and preterm birth, as such risk could depend upon disentangling contributions from drugs versus exposure to maternal psychopathology. The association between the exposure to an AD and an increased risk of *spontaneous abortion* (SA) has not been still clearly established, as conflicting findings have been reported in the studies published [42–44]. A large population-based study on the risk of SA among depressed pregnant women taking different ADs found a

small increased risk associated with the use of AD during pregnancy (RR = 1.6). According to the authors, the risk was likely "related to the underlying maternal depression or to other factors related to the disorder" [45]. Furthermore, there is also evidence indicating that AD use during pregnancy may be associated with neonatal *low birth weight*, even though further investigations, controlling for potential confounding factors, are needed to confirm such adverse outcome [46].

16.2.2.2 Neonatal Adaptation Syndrome

The neonatal adaptation syndrome (NAS) has been frequently described with the use of most ADs, particularly with SSRIs, during the late pregnancy. The incidence rate was found to affect up to 30% of newborns exposed to serotonin reuptake inhibitors (SRIs), i.e. SSRIs and SNRIs, even though other wide estimations were reported (up to 76%), likely because no standardized measurement tool has been so far utilized in the studies published [47]. The aetiology of NAS is still not well understood. Some authors described the NAS as a "withdrawal or abstinence-like syndrome", whilst others supposed a sort of "toxicity reaction", due to an excessive neonatal serotonin in utero exposure. Symptomatology usually is mild and self-limiting and may include tremors, jitteriness or shivering, irritability, cry, insomnia, altered muscle tone, agitation and restlessness, hypoglycaemia, dysregulation of body temperature and poor feeding difficulties. However, only in rare cases, respiratory distress and convulsions have been observed as well. Generally, symptoms begin within the first 2–4 days after delivery and may last for 1 or 2 weeks. It was suggested to minimize such syndrome, to lower the dosage or even to discontinue the drug treatment some weeks before delivery. This practice, however, is nowadays no longer recommended, as lowering the dose before delivery does not seem to avoid such risk, and, in addition, can make the ongoing treatment ineffective for protecting the mother against an early depressive relapse before delivery or in the postpartum period. In most cases, a careful clinical monitoring of newborn and a supportive treatment like advice about regular feeding (particularly breastfeeding) and reassurance are usually adequate for the management of NAS [48, 49]. Moreover, it was found that concomitant exposure to benzodiazepines (BDZs) and SSRIs in pregnancy may result in a higher likelihood of NAS signs that in some cases may persist up to 30 days post-delivery. However, these findings need to be confirmed by further studies [50].

16.2.2.3 Other Neonatal Adverse Outcomes

The risk of having a newborn affected by a *persistent pulmonary hypertension neonatal* (PPHN), a rare but severe respiratory condition, for women treated with ADs (particularly SSRIs) during pregnancy, is still very controversial, as different studies reported contrasting findings [51–54]. Moreover, the entity of risk found was very small (RR ranging from 1.1 to 2.0), with an incidence rate of 3/1000 live newborns in utero exposed to SSRIs, as compared to 2/1000 in unexposed group [51–53]. Furthermore, also a recent "Drug Safety Communication" from the Food and Drug Administration (FDA) and a review on this topic did not found clear evidence to support such association [54].

Less investigations focused on *long-term neurobehavioral outcomes* in children in utero exposed to ADs. In these studies, it is difficult to disentangle the effects of foetal exposure to ADs (or other drugs) from shared maternal-child genetic susceptibility or postnatal environmental factors, such as maternal depression and/or anxiety disorders and their severity. Neonatal motor and cognitive function delays have been associated with maternal use of ADs. However, a systematic review comparing 280 children exposed to ADs, with 291 who were not exposed, did not find significant differences between the two groups in terms of neurocognitive functions. This review also analysed infant "temperament" vs "behaviour", by reporting no significant differences between these variables [55]. In a recent investigation of 34 studies, a small but statistically significant association between prenatal exposure to ADs and some neurodevelopmental outcomes was reported. However, after considering confounding factors, there were no consistent associations between AD exposure and any of the outcome considered [56]. There have been several studies suggesting an association between prenatal AD exposure and *attention-deficit hyperactivity disorder* (ADHD), even though other studies failed to find such association [12, 39]. For example, findings from a Finland National Register-based study did not report a significant association with exposure to SSRIs and ADHD, after controlling for maternal psychiatric illness [57].

The association between SSRIs and the development of *autism spectrum disorders* (ASD) has been a recent topic of systematic reviews and meta-analyses [39]. Even in this case, the results of different investigations are conflicting, so that no firm conclusion can be drawn on such association [58–61]. We agree with Andrade et al. [62, 63], who recently analysed the most relevant data on this issue, that "AD use during pregnancy is likely to be a marker of more severe illness and that inadequately measured, unmeasured or unknown genetic behavioural and/or environmental confounding factors, associated with more severe illness, may be responsible for the increased risk of ASD, rather than the AD exposure by itself", a conclusion that is widely shared by most experts on this topic, who point out that an association does not necessarily imply a causality [11, 12, 39, 49].

16.3 Benzodiazepines and Z-Drugs in Pregnancy

BDZs and Z-drugs (i.e. *zolpidem*, *zopiclone* and *zaleplon*) represent the most prescribed anxiolytics and hypnotic drugs, widely used in the short-term treatment of acute anxiety and insomnia. Studies investigating the drug utilization found that around from 5% to 15% of general population, particularly women, receives the prescription of such drugs [64]. The current widespread use of these medications also in primary care setting has been associated to their increased and uncontrolled long-term use and misuse. For this reason, BDZs must be used only for short-term periods, with a careful and strict clinical monitoring by the physician prescriber, to avoid the risk of developing dependence and abuse.

Anxiety and insomnia represent one of the most frequently occurring psychopathological conditions during the pregnancy, with a prevalence rate estimated from

8% to 12% [65]. These conditions, particularly if severe and persistent, can lead to relevant distress for the pregnant women and, consequently, can cause adverse gestational and neonatal issues [66]. A survey involving about 15,000 pregnant women in 22 countries showed that BDZs were prescribed to 3.0% of them, even though a great variability between countries in prescription rates was observed [67]. Moreover, it has been also reported that around 64–88% of women experience sleep difficulties during pregnancy, compared to 20–38% of women in general population [68]. As there are no consistent data on the prescription and consumption pattern of BDZs and Z-drugs in the perinatal period, it would be desirable to implement training interventions, concerning an adequate utilization of such drugs in routine clinical practice.

16.3.1 Risk of Major Malformations

Among three of six case-control studies published in the 1990s, foetal exposure to BDZs during the first trimester of pregnancy was associated to an increased risk of inducing MMs, particularly oral cleft or cleft lip. However, three cohort studies published in the same period did not find such congenital anomalies [69, 70]. More recently, original cohort studies and systematic reviews indicate that prescribing BZDs in the early pregnancy should not be considered at risk of inducing MMs, including palate and lip defects [71, 72]. A meta-analysis of 9 cohort studies, with over one million analysed pregnancies, including about 4500 newborns exposed in the early pregnancy, reported that BDZs (as a class) do not increase the teratogenic risk [73]. However, in case-control studies, a small increased risk of oral cleft was observed. Moreover, in this investigation, the case-control studies, addressing the specific risk of cardiac MMs, did not detect any statistical significant association to BZD exposure in utero [73].

A cohort study conducted in the UK on about 2000 pregnant women exposed to BDZs in the first trimester reported reassuring data concerning the risk of teratogenicity. The prevalence rate of MMs was between 2.5% and 2.9% in infants exposed to BDZs and Z-drugs and 2.7% in about 19,000 children whose mothers (affected by depression and/or anxiety) did not receive any drug treatment. Risks of system-specific MMs were generally similar in children exposed and not exposed to BDZs [74]. The "non-teratogenic" effect of BDZs, as a pharmacological class, has been also shared by recent overviews and expert opinions, whilst less information is available for each individual BDZ and/or Z-drugs [75].

16.3.2 Risk of Adverse Gestational and Neonatal Outcomes

Foetal exposure to BDZs during the second and third trimester of pregnancy has been associated with an increased risk of a *neonatal withdrawal syndrome* (NWS), a condition affecting about 25% of newborns BDZ-exposed late in pregnancy. NWS

includes signs such as somnolence, irritability, hypoglycaemia, difficulties with sucking, tremors, tachypnoea, gastrointestinal upset, hypoglycaemia and hyperreflexia. It generally appears within a week after delivery and it may last, in some cases, from few days up to few weeks [76]. Tapering the dose of BZDs some weeks before delivery seems not to be effective to avoid neonatal symptoms, and it can induce a maternal withdrawal reaction, especially among women who have been taking high doses of BZDs for several weeks during gestation. Most newborns presenting only a moderate NWS may spontaneously improve after few days, without any long-lasting sequelae. Using BDZs, especially at high doses (given parenterally or intravenously), just before or during the delivery has been associated to an "infant floppy syndrome", characterized by floppiness or general muscular hypotonia at birth or in early life, affecting the limbs, trunk and the cranial-facial musculature. No clear association has been documented between use of BDZ or Z-drugs and gestational adverse outcomes, such as preterm delivery and SA. Moreover, no long-term neurodevelopment anomalies have been observed in infants in utero exposed to BDZ or Z-drugs [12, 72].

16.4 Antipsychotic Drugs in Pregnancy

Antipsychotic (AP) drugs are generally prescribed in the short- and long-term treatment of psychotic disorders, including bipolar disorder. During the last 15 years, there was an increased AP prescription during the pregnancy, particularly for second-generation APs (SGA), as compared with the first-generation APs (FGA) [77]. Less information on the safety profile in pregnancy is available for ziprasidone, lurasidone and cariprazine and for long-acting AP medications (LAI).

16.4.1 Risk of Major Malformations

All APs cross the placenta and can potentially induce congenital MMs in newborns in utero exposed. The ratio of placental passage was found to be highest for olanzapine (72%), followed by haloperidol (65%), risperidone (49%) and quetiapine (23%) [78]. However, these findings do not seem to be related to the rates of MMs reported with these medications. Recent studies indicate that the early foetal exposure to APs, as a class, should not be considered at risk of MMs. In a sample of 1021 pregnant women treated with AP, the rate of birth defects and other gestational and neonatal complications was found not dissimilar to those observed in a control group [79]. In a systematic review focusing on SGA, the average rate of MMs in newborns exposed was 3.5%, a value not significantly different to that reported in general population [80]. In a meta-analysis of 12 studies including about 1800 cases and more than one million of controls, a small but statically significant risk (OR = 2.0) of MMs was found in newborns of women treated with SGA in the first trimester, even though no specific pattern of defects was identified. The authors,

nevertheless, underlined that "further studies sufficiently controlling for confounding factors are needed to validate these findings" [81]. Data from the *National Register Massachusetts General Hospital* showed no significant statistical difference in the rate of MMs between 214 newborns exposed to SGA and a group of 89 unexposed newborns (1.4% vs 1.2%, respectively) [82]. No statistically significant differences were also found in the rate of MMs in a US study comparing about 9000 newborns exposed during gestation to SGA (4.4%) and about 700 exposed to FGA (3.9%). In the unexposed group, the rate was 3.3% [83]. In a review of 59 studies focusing on the risk-benefit of SGA in pregnant women affected by schizophrenia and bipolar disorder, the authors concluded that SGA, as a class, are not associated with an increased risk of congenital birth defects [84]. These findings have been also shared by the most authoritative experts in the perinatal psychopharmacology [11, 12, 85].

16.4.2 Risk of Adverse Gestational and Neonatal Outcomes

Adverse perinatal outcomes, such as SA, preterm birth, low birth weight, small for gestational age, gestational diabetes mellitus and hypertension, have been reported in some studies evaluating women treated with AP (FGA and SGA) during their pregnancy. However, other investigations that used a control group of pregnant women with mental illness, but unexposed to AP or controlled for confounding factors, reported only few or no associations between AP and such perinatal complications [86–88]. Some studies reported that AP exposure during pregnancy was associated with long-term neurodevelopmental delays. However, such association is to be considered with caution, given the lack of reliable studies published so far on this issue [12].

16.5 Mood Stabilizers in Pregnancy

In this section, we shortly discuss the most relevant data coming from studies on the safety of *mood stabilizers* (MS) more frequently prescribed during pregnancy. The prescriptions of MS in a pregnant woman must be carefully evaluated, considering both the perinatal risks of drug exposure and the risk of an untreated SPMI, such as a *bipolar disorder* (BD). Several investigations have documented that bipolar patients if untreated during pregnancy can be at higher risk to develop adverse perinatal outcomes and relapses compared to treated pregnant bipolar women [89]. A study by Viguera et al. [90] reported a relapse rate of 86% in BD pregnant women who discontinued a MS before pregnancy, as compared to 37% of those who maintained the drug treatment. A recent study reported in BD women a significantly higher postpartum relapse rate among those who did not take any medication during their pregnancy (66%), compared to those who were administered a prophylactic MS treatment (23%) [91].

16.5.1 Lithium

Lithium (Li) remains the "gold standard" treatment for the prevention of recurrences and in manic episode of patients with BD. The efficacy of Li in preventing suicidal behaviour in these patients and in those with MDD has been well documented by several controlled studies. Moreover, consistent evidence supported the effectiveness of augmentation strategy of Li in patients with treatment-resistant unipolar depression (TRD) [92]. Moreover, most authoritative experts recommended Li treatment as first-line choice in the prophylactic treatment of bipolar patients, including in women in their childbearing age [93].

16.5.1.1 Risk of Major Malformations

The use of Li in the early pregnancy has been a cause of clinical concern for several years since its introduction in the psychiatric practice. The main reason was related to its potential teratogenicity, particularly that of inducing severe congenital heart defects, such as the *Ebstein's anomaly*, a rare structural defects of tricuspid valve and right ventricle, whose prevalence is now estimated to be 1 in about 21,000 live births [94, 95]. However, recent original studies reported more reassuring findings concerning the foetal safety of Li exposure. A comprehensive review including nine studies (from 1975 to 2018) has been recently published by Poels et al. [96] to establish the safety of Li during pregnancy; three of such studies, particularly, need to be considered for their clinical implications. The first one was published by Diav-Citrin et al. [97] who did not find any statistically significant differences in congenital birth defects (after excluding anomalies that resolved spontaneously), between newborns exposed to Li and a control unexposed group. In the second study, Patorno et al. [98], using data from 1,325,563 pregnancies (US Medicaid), analysed the outcomes of 663 women who were exposed to Li in the first trimester. The results indicated a dose-dependent association between Li and cardiac MMs. The risk of cardiac defects was higher with Li doses above 900 mg/day (RR = 3.2), as compared to doses between 601 and 900 mg/day (RR = 1.6) and to doses less than 600 mg/day (RR = 1.1); the corresponding prevalence rate (per 100/births) of malformations was, respectively, 4.8, 2.1 and 1.6 [98]. Finally, the third investigation was a meta-analysis of 6 cohort studies including 557 pregnancies. Li-exposed group (in the first trimester) was associated with an increased risk of MMs, as compared to controls (prevalence rate: 7.4% vs 4.3%; RR = 1.7), even though no statistically significant differences were reported for cardiac MMs (prevalence rate: 2.1% vs 1.6%) [99].

Overall, during the pregnancy, women treated with Li must be regularly followed with a close monitoring of blood levels, as Li serum levels change across pregnancy and after delivery; blood levels must be checked every 3 weeks for the first 7–8 months and then weekly until the delivery and the first 2 weeks of postpartum period. Foetal echocardiography and a level 2 ultrasound are strongly recommended at 16–18 weeks' gestation [100].

16.5.1.2 Risk of Adverse Gestational and Neonatal Outcomes

Data concerning the safe use of Li during the second–third trimester of pregnancy produced conflicting findings, so that no firm conclusions can be drawn on the lithium's risk of inducing perinatal complications [12]. Infants exposed to Li plasma concentrations more than 0.70 mEq/L, at the time of delivery, could be at risk for low Apgar scores, longer hospital stays and higher CNS and neuromuscular problems ("infant floppy syndrome"), a condition that can be avoided or mitigated by discontinuing Li 24–48 h before planned deliveries or at the onset of labour in spontaneous deliveries. Some studies have also reported cases of neonatal hypotonia, sedation and respiratory distress. Other rare neonatal complications observed in infants exposed in late pregnancy to Li include diabetes insipidus, hypothyroidism, arrhythmias and nephrotoxicity. Information on the long-term neurodevelopmental outcomes in infants exposed prenatally to Li are poor, even though no cognitive or psychomotor impairment has been so far reported [22].

As general rule, women with BD who need lithium maintenance therapy should always be considered a vulnerable, high-risk obstetric population, who would benefit from preconception counselling, regular antenatal care, delivery with neonatal paediatric support and experienced psychiatric management [101].

16.5.2 Anticonvulsant Drugs

Among anticonvulsant MS most of data concerns medications containing *valproate* (e.g. sodium valproate, valproic acid), *carbamazepine* and *lamotrigine*. Moreover, most clinical information regarding the reproductive safety of these drugs come from studies concerning epileptic patients more than women affected by BD.

16.5.2.1 Risk of Major Malformations

Valproate (VLP). Exposure to VLP in monotherapy during the first trimester of pregnancy was associated with an increased rate of MMs (from 6.6% to 17.4%), according to data published by the *EUROCAT Antiepileptic Working Group* [102]. Among the congenital anomalies identified in the study, the risk of *spina bifida* was particularly high (RR = 12.7), as compared to other MMs, such as *hypospadias* (RR = 4.8), *cleft palate* (RR = 5.2) and *cardiac septal defect* (RR = 2.5).

The prevalence rate of spina bifida was around 13 over 10,000 exposed newborns, as compared to 1 over 10,000 of general population. Data from the *EURAP Study Group* and from a Cochrane systematic review have also reported a dose-dependent risk of MMs for VLP, with a rate ranging from 5.6% at doses <700 mg/day to 24.2% for doses > 1500 mg/day [103, 104]. In a large prospective study by Campbell et al. [105], data from 1290 pregnant women exposed to VLP in monotherapy were analysed, and a clear dose-dependent risk of MMs was confirmed: a low risk (about 5–6%) was reported with doses less than 600 mg/day, whilst the MM rate was higher (about 11–12%) with doses above 1000/1500 mg/day [105]. It has been suggested that high dose of folic acid supplementation, before and during pregnancy, could be protective against the risk of spina bifida associated to VLP

exposure in early pregnancy. However, available evidence coming from *North American Birth Defects Registry* does not support this "protective effect", as about 7% of women taking anticonvulsant (including VP) had a child with MM, including defects of neural tube, with and without prenatal folate administration [106]. Given the well-documented risk of teratogenicity associated with high dose of VLP exposure in pregnancy, many regulatory bodies and guidelines across the world (e.g. National Agency for Safety Medicine in France, NICE in the UK) discouraged and even banned the prescription of medications containing VPL during pregnancy and in women of childbearing age, unless no effective alternative drug treatment is available, or unless a pregnancy prevention programme is implemented [12, 107]. Although there is a general agreement on this recommendation, it should be recognized that in patients on the maintenance treatment with VLP, it should be equally considered and the risk associated to VPL treatment and the risk related to discontinuation balanced. Therefore, a careful evaluation of both the risk of teratogenicity (which is dose-dependent) and the risk of treatment discontinuation needs to be discussed with the pregnant woman and her partner, so that an informed and shared decision can be made [108].

Carbamazepine (CBZ). Foetal exposure to CBZ in early pregnancy has been associated in some studies with a small increased risk of congenital MMs, with a prevalence rate from 3.5% to 5%, even though other studies failed to confirm such data [12]. A moderate dose-dependent risk of MMs was documented also for CBZ, with a prevalence rate of around 5% at dosages more than 1000 mg/day; among birth defects, spina bifida was also found, but the risk was smaller than for VLP [105].

Lamotrigine (LMT). Most studies and guidelines indicated that LMT should not be considered at risk of inducing MMs, as the prevalence rate of birth defects reported in the studies published (2–3%) falls within that of general population [11, 12, 105].

16.5.2.2 Risk of Adverse Gestational and Neonatal Outcomes

Valproate. Limited evidence-based information is available on this issue, most of which were obtained from epileptic patients. Gestational adverse outcomes (e.g. preterm delivery, gestational diabetes, spontaneous abortion) and neonatal complications (e.g. low birth weight, hypoglycaemia, withdrawal symptoms, feeding difficulties, admission to neonatal intensive care unit) have been associated, in some studies, with VLP use during pregnancy. However, Bodén et al. [108] did not find significant differences in such perinatal adverse events between 320 bipolar women who were treated with VLP (and other MS) during pregnancy and 534 untreated bipolar women, even though the risk was higher compared with a control group. A neurodevelopmental delay, reduction of IQ scores and increased impaired language acquisition were also reported in children of epileptic mothers treated with VLP during pregnancy. Such risks, as in case of MMs, seem to be dose-related and more severe when VLP is used in association with other anticonvulsant drugs. A systematic review, focusing on the child development in women taking MS in pregnancy, found a dose-response relationship between doses of VLP above 800/1000 mg/day and poorer global cognitive abilities (worsening of the IQ score by 8–11 points).

This finding was not observed for other anticonvulsant MS [109]. The risk of ASD in infants in utero exposed to VLP has been widely investigated in several studies. However, because of methodological flaws in most of studies, no definite conclusion can be drawn on such risk, and further investigations are needed. In fact, it is well known that some maternal diseases in pregnancy have been associated with ASD (e.g. gestational diabetes mellitus, maternal infections), which cause changes in a variety of inflammatory cytokines. In addition, also SSRIs, BDZs, ethanol, cocaine, heavy smoking and air pollution exposure during pregnancy were associated with ASD [110]. A recent cohort study in Denmark including about 900,000 children of epileptic women (90%) has also reported an increased risk (RR = 1.5) of ADHD in infants in utero exposed to VLP (8.4%), as compared to unexposed group (3.2%), with no statistically significant associations found between ADHD and other antiepileptic drugs [111]. However, these findings need to be interpreted with caution and supported by other studies, before drawing definite conclusions.

Carbamazepine and Lamotrigine. As in case of VLP, no consistent findings have been reported concerning the risk of gestational and neonatal complications in women taking CBZ or LMT during pregnancy, even though some cases of such adverse effects were occasionally observed with high doses (e.g. postpartum haemorrhage, induction of labour, SA) [108]. Available evidence does not indicate that CBZ or LMT are associated with infant poorer cognitive development or IQ reduction, as well as with ASD and ADHD [12, 112].

16.6 Psychotropic Drugs During Lactation

Postpartum is a period of psychopathological vulnerability for women, as in the puerperium, physiological changes in hormonal profile may occur, and the new mother may present a greater emotional reactivity and susceptibility to develop psychopathological disorders or exacerbations of a previously psychiatric illness. Breast milk is the only natural food and the main source of nutrition for the newborn, as it contains all the essential factors to ensure an adequate immune protection [113, 114]. Furthermore, the elements of the first feedings (*colostrum*) provide important protective factors for safeguarding the newborn physical health by protecting him from the risk of infections of the lower respiratory and genitourinary tract, reducing also the risk of mortality [114]. The *World Health Organization* (WHO) recommends exclusive breastfeeding in the first 6 months of the infants' life and its continuation during the entire weaning period [113, 114]. Breastfeeding also benefits the new mother by stimulating natural uterine contraction, reducing the physiological postpartum haemorrhage and allowing the uterus to return to normal size faster. Furthermore, breastfeeding favours the development of an appropriate mother-child attachment.

Considering that PD can be excreted into the breast milk at variable degree, safety data on such medications during lactation is essential to minimize infant exposure and potential adverse effects. A number of compounds within the class of PD are nowadays considered safe during breastfeeding, because their concentration

in breast milk is very low or cannot be determined. It has been proposed to assess an acceptable level of drug into breast milk the *relative infant dose* (RID), which estimates the maximum dose of a drug/kg/day that the newborn would theoretically take during breastfeeding. In general, breastfeeding is considered acceptable when the RID is less than 10%. It has been also suggested, as another safety index, to calculate the ratio between the average concentration of drug in breast milk and that in maternal plasma (*milk/plasma ratio*), whose value less than 1 would qualify a drug as safer and thus is recommended in case of breastfeeding [115]. An international updated source of data on the safety of drugs is represented by the *LactMed US database* (LMD). The LMD contains information on drugs to which breastfeeding mothers may be exposed and on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm). Despite reassuring information available for several PDs, mothers may not be encouraged, or perhaps even discouraged, to breastfeed whilst taking such drugs by medical staff for a variety of reasons, including lack of data, safety concern for infants and/or negative attitudes and bias towards mental illness and psychotropics. However, if the mother wishes to breastfeed her baby, the newborn should be monitored in any cases, for the risk of potential, even not severe, adverse effects, with a careful evaluation of the usual neonatal healthy parameters, such as growth curve, body weight and psychomotor development.

16.6.1 Antidepressant Drugs During Lactation

The SRIs are considered the first-line choice among ADs in the treatment of depressive and anxiety disorders during postpartum period. The data on the safety of SRIs in breastfeeding mainly come from case series or cohort studies conducted on small clinical samples. Even though international guidelines suggested that most PDs are "relatively safe" during breastfeeding, further studies should be carried out, considering more large sample with adequate follow-up of breastfed infants [12]. *Sertraline* and *paroxetine* are considered as first-line drugs in women who need an AD medications during breastfeeding, as no relevant adverse reactions have been reported in most infant exposed during breastfeeding; the RID is calculated around 1–2%. Most authoritative reviewers consider sertraline and paroxetine a preferred AD during breastfeeding; moreover, breastfed infants exposed to such drugs during the third trimester of pregnancy have a lower risk of poor neonatal adaptation syndrome than formula-fed infants. The average amount of *fluoxetine* in breast milk is higher than for other SSRI. The active metabolite, norfluoxetine, is detectable in the serum of most breastfed infants during the first 2 months postpartum. Adverse effects such as colic pain, fussiness, irritability and drowsiness have been reported in some breastfed infants. Decreased infant weight gain was found in some case reports, but not in others. No adverse effects on psychomotor development were found in a few infants followed for up to a year of age. Data concerning *citalopram* and *escitalopram* also report relatively reassuring data. A few cases of minor behavioural side effects such as drowsiness or fussiness have been reported, with citalopram, but no adverse

effects on development have been found in infants followed for up to a year. However, infants exposed in utero can have withdrawal effects in the postpartum period despite breastfeeding. Limited information indicates that maternal doses of escitalopram up to 20 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants. One case of necrotizing enterocolitis was reported in breastfed newborn whose mother was taking escitalopram during pregnancy and lactation, but causality was not established. The RID of the drug and its active metabolite is 5.3%. Limited information is available for *fluvoxamine*, indicating that maternal fluvoxamine doses of up to 300 mg daily produce low levels in breast milk and would not be expected to cause any adverse effects in breastfed infants. Low number of cases have been reported with *venlafaxine*; however, data published on the safety of this SNRI (including its active metabolite) seems reassuring, as its RID varies from 4% to 10%. So far, no consistent data have been reported on the safety of *duloxetine* during breastfeeding. A systematic review of SRIs during breastfeeding has been published by Orsolini and Bellantuono [116]. Data concerning the *tricyclics* (TCA), as a class, are less numerous than those of SRIs. However, data are quite reassuring, particularly for *nortriptyline*, as low levels of nortriptyline have been measured in breast milk; amounts ingested by the infant are small and usually not detected in the serum of the infant. Therefore, nortriptyline is considered, among the TCA, the drug of first choice during breastfeeding [18]. Data on the safety use of other ADs (non-SRIs and non-TCA) during breastfeeding is considered still preliminary, due to the low number of infant exposed, so that their utilization in breastfed infants should be avoided.

16.6.2 Benzodiazepines and Z-Drugs During Lactation

BDZs cross the blood-breast barrier and can be detected in breast milk. The greater is the BDZ half-life (t½), the greater the metabolic effort required by newborn to eliminate the drug and, consequently, the risk of BDZ-related side effects. Therefore, shorter-acting BDZs (such as lorazepam, oxazepam and lormetazepam), which have also the advantage of direct hepatic elimination with glucuronic acid, should be preferred to longer-acting ones (such as diazepam, desmethyldiazepam, flurazepam), which undergo more metabolic stages before being eliminated [18, 72]. In a Mother Risk study, *lorazepam* was the most frequently prescribed BDZ during breastfeeding, being reported in about 53% of all BDZ prescribed to 126 women during breastfeeding. The only adverse reaction reported in the study was "sedation", affecting around 1.6% (two cases) of infant exposed to BDZs [117]. From published data, it can be concluded that the sedative effects reported with BDZ exposure through breast milk (at therapeutic doses) may represent a rare risk in infants exposed to such drugs. However, infant sedation is more likely to occur in mothers taking BDZ at higher doses or concomitant CNS depressant drugs during lactation. There are few data on the safety of *non-benzodiazepine hypnotics* (*Z-drugs*) during breastfeeding. Data on *zolpidem*, *zopiclone* and *zaleplon* shows low drug concentrations in breast milk and neonatal serum. However, the

recommendations from guidelines suggest that infants of mother taking such hypnotics, as well as BDZ, during breastfeeding be monitored for the potential, even uncommon, risk of excessive sedation, hypotonia and respiratory depression [12].

16.6.3 Antipsychotic Drugs During Lactation

Overall, both FGA and SGA are not contraindicated during lactation. Data concerning some FGA like *haloperidol*, *chlorpromazine*, *perphenazine*, *trifluoperazine* and *flupentixol* are reassuring, as the amount of drug detected in serum of breastfed infant is low (RID less than 10%). Also, drugs belonging to the SGA, particularly *olanzapine*, *quetiapine*, *risperidone/paliperidone* and *aripiprazole*, are considered not at risk of inducing relevant infant adverse effects during breastfeeding. Moreover, the concentration of drug in infants is low or undetectable and the milk/plasma ratio is below 0.5%. The RID calculated for SGA widely ranges from 0.1% to 4% for quetiapine and olanzapine whilst from 2% to 9% for aripiprazole and risperidone. *Clozapine* is an exception, because it is considered contraindicated during breastfeeding, due to the risk of infant agranulocytosis and seizure, even though the RID is low (1.4%) [18]. Few case reports observed a neurodevelopmental delay in infants exposed to APs, as a class, during the breastfeeding, but there were no controlled studies, and the impact of underlying maternal disease was not taken into account. In addition, considering the few data published, no firm conclusion can be made on this issue [12]. Overall, according to the recent guidelines, it should be recommended that women who need to be treated during postpartum period with antipsychotic medications should not be discouraged from breastfeeding. As general rule, a clinical monitoring is always recommended in infants breastfed by mothers taking AP medications.

16.6.4 Mood Stabilizers During Lactation

16.6.4.1 Lithium

Li excretion into breast milk and concentrations in infant serum are highly variable; the RID estimates vary, with value of up 42% being reported with Li carbonate. No data are available with lithium one-a-day formulations (“slow release”). Although Li appears on some lists of drugs contraindicated during breastfeeding, many sources do not consider it an absolute contraindication. Several case reports did not document in infants who were breastfed during Li therapy, the emergence of symptoms of toxicity or developmental anomalies. Most infants were breastfed from birth and some continued to nurse for up to 1 year of maternal lithium therapy. However, Li during, in those cases in which there is a renal impairment and/or an impaired Li elimination, such as in neonatal dehydration, infections or prematurity. Occasionally, symptoms like hypothermia, hypotonia, lethargy and T-wave modifications at ECG were observed in infants of mothers taking lithium during postpartum period. On the bases of available evidence, Li (in monotherapy) may be used in

mothers of full-term newborns who are willing and able to monitor their infants. Because maternal Li requirements and dosage may be increased during pregnancy, maternal serum levels should be monitored frequently in the postpartum period and dosage reduced as necessary, to avoid excessive infant exposure via breast milk. It is also recommended, during breastfeeding, a regular monitoring of infant's Li serum levels, creatininemia, blood urea and TSH. A recent overview of Li safety during lactation is reported by Uguz and Orsolini [18].

16.6.4.2 Anticonvulsant Drugs

VLP levels in breast milk are low and infant serum levels range from undetectable to very low. Breastfeeding during VPA monotherapy does not appear to adversely affect infant growth or development, and one study reported that breastfed infants had higher IQs and enhanced verbal abilities than no breastfed infants at 6 years of age. If VLP is required by the mother during puerperium, there is not a reason to discontinue breastfeeding. No definite adverse reactions to VLP in breastfed infants have been reported. It is in any case a good practice that infants should be monitored for jaundice and other signs of liver damage during breastfeeding. Some authors also recommended the monitoring of infant serum VLP levels, platelets and liver enzymes. Treatment with VLP in association with sedating anticonvulsants or PD can result in risk of infant sedation or withdrawal reactions.

CBZ breastfeeding in monotherapy does not appear to adversely affect infant growth or development. Moreover, it has been documented that breastfed infants had higher IQs and enhanced verbal abilities than no breastfed infants at 6 years of age. Generally, if CBZ is required by the mother, there are no reasons to discontinue breastfeeding. However, a few cases of sedation, poor sucking, withdrawal reactions and hepatic dysfunction have been reported. It is also suggested the monitoring of infant serum CBZ levels, liver enzymes and a complete blood count during breastfeeding. Combination of CBZ with other anticonvulsants or PD should be avoided during breastfeeding.

LMT high concentrations are detectable in breast milk few hours after the intake of drug by nursing mother. The maternal serum level of infant exposed via breast milk is approximately around 30–50%. In a study including 30 infants exposed during breastfeeding to CBZ (maternal dose ranging from 50 to 800 mg/day), the mean milk/plasma ratio reported was 41%. However, breastfeeding during LMT monotherapy does not appear to adversely affect infant growth or development, even though some cases of apnoea and CNS depression have been observed. LMT monotherapy may be considered relatively safe during lactation, but a regular monitoring of plasma level and platelet counts of nursing infant is recommended [18].

16.7 Conclusion and Clinical Implications

An early and careful planning for the PD treatment in pregnancy should be made before the women become pregnant. More than 50% of pregnancies are unplanned and, hence, psychiatrists need to make treatment decision for women who are

already pregnant. As general approach, the prescription of PD during pregnancy should take into consideration several factors, such as the patient's psychiatric and psychopharmacological history, the severity of symptoms, the neonatal safety of drug prescribed and the attitude of pregnant women towards PD use. The main priority should be to keep the pregnant women in a good mental health state, as severe psychopathological conditions are a well-established risk factor for the mother, the gestation and the offspring. Nowadays, more accurate information, coming from cohort studies and meta-analyses, are available for clinicians to allow a proper assessment of the safety profile of most commonly prescribed PD during pregnancy [18]. In any cases, the decision to maintain or to start with a new drug treatment must be carefully evaluated by the specialist prescriber and the prescription shared with the pregnant woman and her partner, through a detailed informed consent [17]. Also, during the postpartum period, the decision to start or to maintain a PD treatment needs to be taken on the basis of recent available evidences on the drug safety in breastfeeding, evaluating the available safety parameters. There is some evidence that women very often overestimate PD teratogenic and other perinatal risks and that evidence-based counselling can enable them to restart such drugs, when needed. Thus, it is crucial that mental health professionals, in generic service, need to be trained with to "think family", so that they can deliver care, including drug treatment, with a life course lens, having pregnancy and family in mind [118].

References

1. Biaggi A, Conroy SB, Pawlby S, et al. Identifying the women at risk of antenatal anxiety and depression: A systematic review. J Affect Disord. 2016;191:62–77.
2. ACOG Committee Opinion No. 757. Screening for Perinatal Depression. Obstet Gynecol. 2018;132:e208–12.
3. National Institute of Mental Health (NICE). The perinatal mental health care pathways. National Collaborating Centre for Mental Health London. 2018;
4. Grigoriadis S, Graves L, Peer M, et al. Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry. 2018;79(5):17r,1201.
5. Orsolini L, Valchera A, Vecchiotti R, et al. Suicide during perinatal period: epidemiology, risk factors, and clinical correlates. Front Psychiatry. 2016;7:138.
6. Gressier F, Guillard V, Cazas O, et al. Risk factors for suicide attempt in pregnancy and the postpartum period in women with serious mental illnesses. J Psychiatr Res. 2017;84:284–91.
7. Wisner KL. The last therapeutic orphan: the pregnant woman. Am J Psychiatry. 2012;169:554–6.
8. Andrade C. A primer on confidence intervals in psychopharmacology. J Clin Psychiatry. 2015;76(2):228–31.
9. Nonacs RM, Cohen L. Challenges in determining outcomes of prenatal exposure to antidepressants. J Clin Psychiatry. 2020;81(3):20com13269.
10. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007;356(26):2675–83. Erratum in: N Engl J Med 2015; 373(7): 686
11. Chisolm MS, Payne JL. Management of psychotropic drugs during pregnancy. BMJ. 2016;532:h5918.

12. McAllister-Williams RH, Baldwin DS, Cantwell R., Endorsed by the British Association for Psychopharmacology et al.; British Association for Psychopharmacology (BAP) consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum. J Psychopharmacol 2017; 31(5): 519–552.
13. Alwan S, Bérard A. Chapter 1. Epidemiology of the use of psychotropic drugs in pregnancy and nursing women. In: Uguz F, Orsolini L, editors. Perinatal psychopharmacology. Berlino: Springer; 2019.
14. Ram D, et al. Psychopharmacoteratophobia: excessive fear of malformation associated with prescribing psychotropic drugs during pregnancy: an Indian perspective. Indian J Pharmacol. 2015;47(5):484–90.
15. Huybrechts KF, Palmsten K, Mogun H, Kowal M, Avorn J, Setoguchi-Iwata S, Hernández-Díaz S. National trends in antidepressant medication treatment among publicly insured pregnant women. Gen Hosp Psychiatry. 2013;35:265–71.
16. Shivakumar G, Kroll-Desrosiers AR, Copeland L, Anderson EH, Maydon A, Mattocks K. Patterns of treatment utilization across the perinatal period in the center for maternal and infant outcomes and research in translation (COMFORT) veterans study. J Womens Health (Larchmt). 2020; https://doi.org/10.1089/jwh.2020.8435.
17. Bellantuono C, Martellini M, Orsolini L. Chapter 4. General approach to pharmacological treatment during the perinatal period. In: Uguz F, Orsolini L, editors. Perinatal psychopharmacology. Berlino: Springer; 2019.
18. Uguz F, Orsolini L. Perinatal psychopharmacology. 1st ed. Berlino: Springer; 2019.
19. Molenaar MN, Lambregtse-van den Berg PT, Bonsel GJ. Dispensing patterns of SSRIs before, during and after pregnancy: a 16-year population-based cohort study from the Netherlands. Arch Women's Mental Health. 2020;23(1):71–9.
20. Jimenez-Solem E, Andersen JT, Petersen M, et al. Prevalence of antidepressant use during pregnancy in Denmark, a nation-wide cohort study. PLoS One. 2013;8(4):e63034.
21. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol. 2011;205(51):e51–51.e58.
22. Betcher HK, Wisner KL. Psychotropic treatment during pregnancy: research synthesis and clinical care principles. J Womens Health (Larchmt). 2020;29(3):310–8. https://doi.org/10.1089/jwh.2019.778.
23. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006;295:499–507.
24. National Institute for Health and Care Excellence (NICE) 2015 Antenatal and postnatal mental health: Clinical management and service guidance. NICE Guidelines CG192. Available at: https://www.nice.org.uk/guidance/CG192.
25. Centers for Disease Control and Prevention. World birth defects day, 2018. Available at: https://www.cdc.gov/features/birth-defects-day.
26. Kallen BA, Otterblad OP. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol. 2007;79:301–8.
27. Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med. 2010;40:1723–33.
28. Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to SSRI and risk of MM: a nationwide cohort study. BMJ Open. 2012;2:e001148. https://doi.org/10.1136/bmjopen-2012-0011.
29. Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol. 2011;118:111–20.
30. Ban L, Gibson JE, West J, et al. Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study. BJOG. 2014;121(12):1471–81. https://doi.org/10.1111/1471-0528.12682.
31. Wang S, Yang L, Wang L, Gao L, Xu B, Xiong Y. Selective Serotonin Reuptake Inhibitors (SSRIs) and the risk of congenital heart defects: a meta-analysis of prospective cohort studies. J Am Heart Assoc. 2015;4(5):e001681. https://doi.org/10.1161/JAHA.114.001681.

32. Huybrechts KF, Hernandez-Diaz S, Avorn J. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med. 2014;371:1168–9.
33. Petersen I, Evans SJ, Gilbert R, et al. Selective serotonin reuptake inhibitors and congenital heart anomalies: comparative cohort studies of women treated before and during pregnancy and their children. J Clin Psychiatry. 2016;77(1):e36–42.
34. Gentile S, Bellantuono C. Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of fetal major malformations: focus on paroxetine. J Clin Psychiatry. 2009;70:414–22.
35. Riggin L, Frankel Z, Moretti M, Pupco A, Koren G. The fetal safety of fluoxetine: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2013;35:362–9.
36. Bellantuono C, Vargas M, Mandarelli G, et al. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. Hum Psychopharmacol. 2015;30(3):143–51.
37. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ. 2015;350:h1798.
38. Lassen D, Ennis ZN, Damkier P. First-trimester pregnancy exposure to venlafaxine or duloxetine and risk of major congenital malformations: a systematic review. Basic Clin Pharmacol Toxicol. 2016;118(1):32–6. https://doi.org/10.1111/bcpt.12497.
39. Grigoriadis S, Peer M. Antidepressants in pregnancy. In: Uguz F, Orsolini L, editors. Perinatal psychopharmacology. Springer; 2019.
40. Wisner KL, Sit DK, Hanusa BH, et al. Major depression and antidepressant treatment: Impact on pregnancy and neonatal outcomes. Am J Psychiatry. 2009;166:557–66.
41. Malm H, Sourander A, Gissler M, et al. Pregnancy complications following prenatal exposure to SSRIs or maternal psychiatric disorders: results from population-based national register data. Am J Psychiatry. 2015;172:1224–32.
42. Nakhai-Pour HR, Broy P, Berard A. Use of antidepressants during pregnancy and the risk of spontaneous abortion. CMAJ. 2010;182:1031–7.
43. Einarson A, Choi J, Einarson TR, Koren G. Rates of spontaneous and therapeutic abortions following use of antidepressants in pregnancy: results from a large prospective database. J Obstet Gynaecol Can. 2009;31:452–6.
44. Einarson A. Antidepressants and pregnancy: complexities of producing evidence-based information. CMAJ. 2010;182:1017–8.
45. Kjaersgaard MI, Parner ET, Vestergaard M, et al. Prenatal antidepressant exposure and risk of spontaneous abortion—a population-based study. PLoS One. 2013;8(8):e72095.
46. Prady SL, Hanlon I, Fraser L, et al. A systematic review of maternal antidepressant use in pregnancy and short- and long-term offspring's outcomes. Arch Women's Mental Health. 2018;21(2):127–40.
47. Galbally M, Spigset O, Johnson AR, Kohan R, Lappas M, Lewis AJ. Neonatal adaptation following intrauterine antidepressant exposure: assessment, drug assay levels, and infant development outcomes. Pediatr Res. 2017;82(5):806–13. https://doi.org/10.1038/pr.2017.156.
48. Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry. 2013;74:e309–20.
49. Vigod SN, Wilson CA, Howard LM. Depression in pregnancy. BMJ. 2016;352:i1547. https://doi.org/10.1136/bmj.i1547.
50. Salisbury AL, O'Grady KE, Battle CL, et al. The roles of maternal depression, serotonin reuptake inhibitor treatment, and concomitant benzodiazepine use on infant neurobehavioral functioning over the first postnatal month. Am J Psychiatry. 2016;173:147–57.
51. Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, Gopalakrishnan C, Levin R, Mogun H, Hernandez-Diaz S. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA. 2015;313:2142–51.

52. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf. 2009;18(3):246–52.
53. Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. Am J Perinatol. 2011;28(1):19–24.
54. Lusskin SI, Khan SJ, Ernst C, Habib S, Fersh ME, Albertini ES. Pharmacotherapy for perinatal depression. Clin Obstet Gynecol. 2018;61(3):544–61. https://doi.org/10.1097/GRF.0000000000000365.
55. Pedersen LH, Henriksen TB, Bech BH, Licht RW, Kjaer D, Olsen J. Prenatal antidepressant exposure and behavioral problems in early childhood--a cohort study. Acta Psychiatr Scand. 2013;127:126–35.
56. Rommel AS, Bergink V, Liu X, Munk-Olsen T, Molenaar NM. Long-term effects of intrauterine exposure to antidepressants on physical, neurodevelopmental, and psychiatric outcomes: a systematic review. J Clin Psychiatry. 2020;81(3):19r12965. https://doi.org/10.4088/JCP.19r12965.
57. Malm H, Brown AS, Gissler M, et al. Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J Am Acad Child Adolesc Psychiatry. 2016;55:359–66.
58. Man KK, Tong HH, Wong LY, Chan EW, Simonoff E, Wong IC. Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: a systematic review and meta-analysis of observational studies. Neurosci Biobehav Rev. 2015;49:82–9.
59. Castro VM, Kong SW, Clements CC, et al. Absence of evidence for increase in risk for autism or attention deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. Transl Psychiatry. 2016;6:e708.
60. Andrade C. Antidepressant use in pregnancy and risk of autism spectrum disorders: a critical examination of the evidence. J Clin Psychiatry. 2013;74:940–1.
61. Hagberg KW, Robijn AL, Jick S. Maternal depression and antidepressant use during pregnancy and the risk of autism spectrum disorder in offspring. Clin Epidemiol. 2018;10:1599–612.
62. Andrade C. Antidepressant exposure during pregnancy and risk of autism in the offspring, 2: do the new studies add anything new? J Clin Psychiatry. 2017;78(8):e1052–6.
63. Andrade C. Genes and unmeasured and unknown confounds in studies of neurodevelopmental outcomes after antidepressant prescriptions during pregnancy. J Clin Psych. 2020;81(3):20f13463.
64. Gentile S. Anxiety and sleep disorders, psychopharmacology, and pregnancy. In: Galbally M, Snellen M, editors. Psychopharmacology and pregnancy. Treatment efficacy, risks, and guidelines. Berlin Heidelberg: Springer-Verlag; 2014.
65. Goodman JH, Chenausky KL, Freeman MP. Anxiety disorders during pregnancy: a systematic review. J Clin Psychiatry. 2014;75(10)
66. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Tomlinson G, Vigod SN, Dennis CL, Steiner M, Brown C, Cheung A, Dawson H, Rector NA, Guenette M, Richter M. Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry. 2018;79(5):17r12011. https://doi.org/10.4088/JCP.17r12011.
67. Bellantuono C, Tofani S, Di Sciascio G, Santone G. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. Gen Hosp Psychiatry. 2013;35:3–8.
68. Ban L, West J, Gibson JE, Fiaschi L, Sokal R, Doyle P, Hubbard R, Smeeth L, Tata LJ. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One. 2014;9(6):25.
69. Dolovich LR, Addis A, Regis JM, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case–control studies. BMJ. 1998;317:839–43.
70. Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the foetus, the neonate, and the nursing infant. Psychiatr Serv. 2002;53:39–49.

71. Bais B, Molenaar NM, Bijma HH, Hoogendijk WJG, Mulder CL, Luik AI, Lambregtse-van den Berg MP, Kamperman AM. Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: a systematic review and meta-analysis. J Affect Disord. 2020;269:18–27. https://doi.org/10.1016/j.jad.2020.03.014.
72. Bellantuono C, Martellini M, Orsolini L. Chapter 12. Benzodiazepines and Z-Drugs during pregnancy. In: Uguz F, Orsolini L, editors. Perinatal psychopharmacology. Springer; 2019.
73. Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. J Obstet Gynaecol Can. 2011;33(1):46–8.
74. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Ruthirakuhan M, Chan P, Hennawy M, Parikh S, Vigod SN, Dennis CL, Steiner M, Brown C, Cheung A, Dawson H, Rector N, Guenette M, Richter M. Pregnancy and delivery outcomes following benzodiazepine exposure: a systematic review and meta-analysis. Can J Psychiatr. 2020;65(12):821–34. https://doi.org/10.1177/0706743720904860.
75. Wikner BN, Källén B. Are hypnotic benzodiazepine receptor agonists teratogenic in humans? J Clin Psychopharmacol. 2011;31:356–9.
76. Smirk CL, Bowman E, Doyle LW, Kamlin CO. How long should infants at risk of drug withdrawal be monitored after birth? J Paediatr Child Health. 2014;50(5):352–1.
77. Uguz F. Pharmacological prevention of mood episodes in women with bipolar disorder during the perinatal period: a systematic review of current literature. Asian J Psychiatr. 2020;52:102145. https://doi.org/10.1016/j.ajp.2020.102145.
78. Poels EMP, Schrijver L, Kamperman AM, Hillegers MHJ, Hoogendijk WJG, Kushner SA, Roza SJ. Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2018;27(9):1209–30. https://doi.org/10.1007/s00787-018-1177-1.
79. Vigod SN, Gomes T, Wilton AS, et al. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. BMJ. 2015;350:h2298.
80. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. Basic Clin Pharmacol Toxicol. 2015;116(4):315–20.
81. Terrana N, Koren G, Pivovarov J, et al. Pregnancy outcomes following in utero exposure to second-generation antipsychotics: a systematic review and meta-analysis. J Clin Psychopharmacol. 2015;35(5):559.
82. Cohen LS, Viguera AC, McInerney KA, Freeman MP, Sosinsky AZ, Moustafa D, Marfurt SP, Kwiatkowski MA, Murphy SK, Farrell AM, Chitayat D, Hernández-Díaz S. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Am J Psychiatry. 2016;173(3):263–70. https://doi.org/10.1176/appi.ajp.2015.15040506.
83. Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry. 2016;73(9):938–46.
84. Tosato S, Albert U, Tomassi S, et al. A systematized review of atypical antipsychotics in pregnant women: Balancing between risks of untreated illness and risks of drug-related adverse effects. J Clin Psychiatry. 2017;78(5):e477–89.
85. Breadon C, Kulkarni J. Antipsychotic in pregnancy. In: Uguz F, Orsolini L, editors. . Perinatal psychopharmacology, Springer; 2019.
86. Bodén R, Lundgren M, Brandt L, et al. Antipsychotics during pregnancy: relation to fetal and maternal metabolic effects. Arch Gen Psychiatry. 2012;69(7):715–21.
87. Lin HC, Chen IJ, Chen YH, et al. Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? Schizophr Res. 2010;116(1):55–60.
88. Petersen I, McCrea RL, Sammon CJ, et al. Risks and benefits of psychotropic medication in pregnancy: Cohort studies based on UK electronic primary care health records. Health Technol Assess. 2016;20:1–176.
89. Sharma V, Pope CJ. Pregnancy and bipolar disorder: a systematic review. J Clin Psychiatry. 2012;73(11):1447–55. https://doi.org/10.4088/JCP.11r07499.

90. Viguera AC, Newport DJ, Ritchie J, et al. Lithium in breast milk and nursing infants: clinical implications. Am J Psychiatry. 2007;164:342–5.
91. Wesseloo R, Kamperman AM, Munk-Olsen T, et al. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. Am J Psychiatry. 2016;173:117–2.
92. Tondo L, Alta M, Bauer M, et al. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. 2019;7:16.
93. Bergink V, Kushner SA. Lithium during pregnancy. Am J Psychiatry. 2014;171(7):712–5.
94. Weinstein MR, Goldfield M. Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry. 1975;132:529–31.
95. Boyle B, Garne E, Loane M, et al. The changing epidemiology of Ebstein's anomaly and its relationship with maternal mental health conditions: a European registry-based study. Cardiol Young. 2017;27(4):677–85.
96. Poels EMP, Bijma HH, Galbally M, Bergink V. Lithium during pregnancy and after delivery: a review. Int J Bipolar Disord. 2018;6(1):26. https://doi.org/10.1186/s40345-018-0135-7.
97. Diav-Citrin O, Shechtman S, Tahover E, et al. Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. Am J Psychiatry. 2014;171(7):785–94.
98. Patorno E, Huybrechts KF, Hernandez-Diaz S. Lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med. 2017;377(9):893–4. https://doi.org/10.1056/NEJMc1708919.
99. Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, Gomes T, Howard LM, Khalifeh H, Krohn H, Larsson H, Lichtenstein P, Taylor CL, Van Kamp I, Wesseloo R, Meltzer-Brody S, Vigod SN, Bergink V. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018;5(8):644–52. https://doi.org/10.1016/S2215-0366(18)30180-9.
100. Wesseloo R, Wierdsma A, Hoogendijk WJ, et al. Lithium dosing during pregnancy. Br J Psychiatry. 2017;211:31–6.
101. Frayne J, Nguyen T, Mok T, Hauck Y, Liira H. Lithium exposure during pregnancy: outcomes for women who attended a specialist antenatal clinic. J Psychosomatic Obste Gynecol. 2018;39(3):211–9.
102. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van den Berg LT, EUROCAT Antiepileptic Study Working Group. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med. 2010;362(23):2185–93.
103. Tomson T, Battino D, Bonizzoni E, EURAP Study Group, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology. 2015;85(10):866–72.
104. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;11(11):CD010224. https://doi.org/10.1002/14651858.CD010224.pub2.
105. Campbell E, Kennedy F, Russell A, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry. 2014;85(9):1029–34.
106. Patel N, Viguera AC, Baldessarini RJ. Mood-stabilizing anticonvulsants, spina bifida, and folate supplementation: commentary. J Clin Psychopharmacol. 2018;38(1):7–10. https://doi.org/10.1097/JCP.0000000000000813.
107. Andrade C. Valproate in pregnancy. J Clin Psychiatry. 2018;79(3):18f12351.
108. Bodén R, Lundgren M, Brandt L, et al. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ. 2012;345:e7085.
109. Haskey C, Galbally M. Mood stabilizers in pregnancy and child developmental outcomes: a systematic review. Aust NZ J Psychiatry. 2017;51(11):1087–97. https://doi.org/10.1177/0004867417726175.

110. Araujo JSA, Delgado IF, Paumgartten FJR. Antenatal exposure to antidepressant drugs and the risk of neurodevelopmental and psychiatric disorders: a systematic review. Cad Saude Publ. 2020;36(2):e00026619. https://doi.org/10.1590/0102-311X00026619.
111. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. JAMA Netw Open. 2019;2(1):e186606. https://doi.org/10.1001/jamanetworkopen.2018.6606. Erratum in: JAMA Netw Open. 2019;2(2):e191243
112. McCorry D, Bromley R. Does in utero exposure of antiepileptic drugs lead to failure to reach full cognitive potential? Seizure. 2015;28:51–6.
113. World Health Organization (WHO). Long-term effects of breastfeeding—a systematic review. Geneva: WHO; 2013. Available at: http://apps.who.int/iris/bitstream/10665/79198/1/9789241505307_eng.pdf?ua=1
114. World Health Organization (WHO). Short-term effects of breastfeeding—a systematic review. Geneva: WHO; 2013. Available at: http://apps.who.int/iris/bitstream/10665/79198/1/9789241505307_eng.pdf?ua=1
115. Hale TW, Kendall-Tackett K, Cong Z, Votta R, McCurdy F. Discontinuation syndrome in newborns whose mothers took antidepressants while pregnant or breastfeeding. Breastfeed Med. 2010;5(6):283–8.
116. Orsolini L, Bellantuono C. Serotonin reuptake inhibitors and breastfeeding: a systematic review. Hum Psychopharmacol. 2015;30(1):4–20.
117. Kelly LE, Poon S, Madadi P, Koren G. Neonatal benzodiazepines exposure during breastfeeding. J Pediatr. 2012;161(3):448–51.
118. Howard LM, Khalifeh H. Perinatal mental health: a review of progress and challenges. World Psychiatry. 2020;19:313–27.