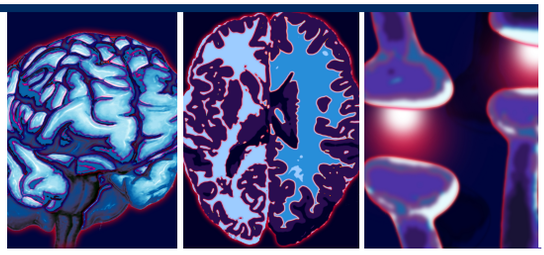
REVIEW



Pregnancy and postpartum in bipolar disorder

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Practice points

- Risk of having small for gestational age/low birth weight infant and preterm births seems to be increased in bipolar disorder. However, the number of studies is limited and the potential roles of lifestyle and medication use on these findings are not clearly known.
- The rates of recurrences during pregnancy are high. It is evident particularly after abrupt discontinuation of the ongoing medication. The sole effect of pregnancy on the recurrences is currently not clear.
- The clinician should weigh the high risk of recurrence and morbidity associated with discontinuing maintenance mood stabilizer treatment versus the risks of fetal exposure to mood stabilizers.
- Continuing lithium may be an option with close fetal cardiac monitorization. However, avoidance from valproate is suggested. Safety data on the atypical antipsychotics remains inconclusive. Selective serotonin reuptake inhibitors as a class were not significantly associated with increased risk of either minor congenital malformations or cardiac malformation. However, attention should be paid for individual antidepressants. There is no specific recommendation on the medication selection.
- When necessary, using medications as monotherapy at minimal effective doses is preferable. Priority should be given to medications with potential efficacy in preventing postpartum mood episodes.
- The increased risk of illness recurrence during postpartum period is evident. Misdiagnosis of bipolar II disorder as a major depressive disorder in this period is a serious risk.
- Bipolarity should be considered during postpartum in the following conditions: depression starting immediately after childbirth; having atypical and mixed features, racing thoughts, psychosis during depression or occurrence of psychosis in a wider sense; poor response to medication or switching to (hypo)mania with antidepressant use and family history for bipolar disorder. The clinician should also be aware of postpartum hypomania.
- Sleep hygiene during pregnancy and particularly postpartum is crucial in preventing recurrences.

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Future Medicine part of fsg

SUMMARY Pregnancy and postpartum pose a challenge for the illness course and treatment in bipolar disorder (BD). This article reviews the most updated data on the pregnancy and birth outcomes and child-bearing related course of illness together with treatment during pregnancy in BD. Two electronic databases, MEDLINE and SCOPUS were searched for the child-bearing related clinical studies and systematic reviews published in English. The reference lists of identified publications were also searched for other relevant publications. Data from a limited number of studies reveal an increased risk for small for gestational age and preterm births in women with BD. The results are inconclusive owing to the potential confounders, such as lifestyle and medication. Despite repeatedly reported high rates of episode recurrences during pregnancy, the exact impact of pregnancy on the course of illness in BD is equivocal. However, abrupt medication discontinuation sets a definite risk factor for significantly increased episode recurrences during pregnancy. Continuing lithium may be an option with a close fetal cardiac monitorization. However, avoidance from valproate is suggested. Safety data on the atypical antipsychotics remains inconclusive. There is no specific recommendation on the medication selection. Pregnancy is an event that may intersect the treatment course in women with BD. The exact impact of pregnancy on the course of BD and its subtypes is still to be explored, as is the role of confounding factors such as lifestyle and medication use on the adverse course of illness and birth outcomes.

Bipolar disorder (BD) is a chronic illness with a relapsing and remitting course. Symptoms in BD involve various domains, such as mood, energy, motor activity, sleep, appetite, thought and cognition. Mania is the core feature of the illness that gives rise to the definite diagnosis [1]. BD I, BD II and BD not otherwise specified (BDNOS) are the three subtypes of illness. BD I is characterized by recurrent episodes of mania and depression, while BD II is defined as recurrent episodes of depression and hypomania [1]. Prevalence of BD I and II together ranges between 0.4–4.5% [2,3].

BD is one of the most debilitating illnesses and the sixth leading cause of work disability worldwide [4,5]. In a considerably high proportion of individuals, the illness onset is before the age of 18 years [6–8,101]. Misdiagnosis is frequent, reaching up to 69% [9] and recurrence rates despite drug treatment are high with a 2-year recurrence rate of 50% and a 5-year recurrence rate of 70–90% [2–4]. At least 50% of patients suffer from significant residual symptoms which pose a fourfold higher risk for a major mood episode. The patients with BD spend most of their time in a depressed state [10]. Significant rates of nonadherence with medications, often for psychological reasons play an important role in the adverse course of illness [4,9,11–13].

The disorder is associated with substantial risk of long-term morbidity, comorbidity and severe functional impairments, including high rates of family or marital problems [4,14–18] and suicide attempts reaching up to 36.3 and 32.4% in BD I and BD II, respectively [19].

Reproductive events have a substantial impact on the course of BD. The onset of illness occurs before or within 1 year of menarche in a considerably high proportion of the females with BD [20]; therefore, optimal treatment for most women with BD includes mood stabilizers for most of their reproductive years. The initiation of the proper treatment may be delayed until after having children, mainly due to the fact that the overt appearance of the illness occurs in the postpartum period. In several longitudinal studies, the postpartum psychosis was shown not to be a discrete nosologic entity, but a postpartum presentation of an underlying mood disorder that appears mainly within the bipolar spectrum [21,22]. A more recent register-based cohort study of a long-term follow-up of a total of 120,378 women with a first-time psychiatric inpatient or outpatient admission with any type of psychiatric disorder revealed a predictive effect of symptoms occurring within the first 14 days of delivery on the subsequent conversion to BD (relative risk: 4.26; 95% CI: 3.11–5.85) [23].

Clinical management of women with mood disorders during perinatal periods is a complex issue that highlights the need for balancing potential teratogenic and other adverse effects of medication on the child, against the consequences of potentially life-threatening untreated maternal illness on fetal and neonatal development [24–27].

Recently, it has been suggested that pregnancies in women with BD, including those that are not planned, need to be conceptualized as

expected events that intersect with treatment course [28].

Awareness on how the medication and mood conditions may influence the pregnancy outcome and child development is of key importance on the pregnancy-related major decisions that both clinicians and patients have to make. Nearly half of bipolar women at reproductive age are reported to be advised to avoid pregnancy by a healthcare professional, mainly by a psychiatrist [29]. An earlier study reported a high rate (39%) of remaining childless in 85 lithium responder women [30]. The fear of adverse effects of medicines on fetal development and fear of illness recurrence if maintenance treatment were discontinued were shown to be highly prevalent among bipolar women who avoid pregnancy even after a specialized consultation on treatment options and risks of pregnancy in BD [29].

More than half of pregnant women with bipolar and unipolar mood disorder are reported to discontinue their mood disorder medication during pregnancy, although, women with BD were more concerned than those with a unipolar condition about the potential impact of pregnancy on their mood, as well as the potential for their offspring to inherit a mood condition [31]. The given finding is a reflection of the limited knowledge on morbidity risks and optimal treatment of women with major psychiatric illnesses during pregnancy, at childbirth, and during the postpartum period, particularly with BD [24,32–34].

This review aims to present the most updated data on the effect of maternal BD on the offspring, childbearing-related course of illness which covers pregnancy and postpartum and the treatment during pregnancy in women with BD.

Method

Literature search was completed through the electronic databases MEDLINE/PubMed and SCOPUS by using combination of the following keywords: BD, pregnancy, outcome, mood disorders, treatment, lithium, mood stabilizers, pharmacotherapy and postpartum. The reference lists of publications identified were also searched to select other relevant publications. Child-bearing related clinical studies and systematic reviews published in English were included. Data on the postpartum period was included only in the section where course of illness is reviewed. Owing to the intensity of pharmacological considerations, treatment during postpartum has been kept beyond the scope of the present review.

Results

■ Pregnancy & birth outcomes in BD

Data on the pregnancy and birth outcomes in BD come from limited number of studies that have been published during the past decade.

A relatively early study [35] analyzed prospectively recorded obstetric data of 3174 births by 1831 women with schizophrenia, unipolar depression and BD during 1980–1992. With reference to the randomly selected women without a psychiatric diagnosis, who had given birth to 3129 children during the same time period women with schizophrenia and BD, particularly those with illness onset prior to the child bearing were significantly more likely to experience placental abnormalities, ante partum hemorrhages and drug toxic side effects (owing to alcohol, tobacco and illicit substances). During labor, all three diagnostic groups were more likely to experience fetal distress. Infants born to mothers with BD did not present low birth weight (LBW). However, the study is lacking exact data on smoking and specific information on prescription medications or illicit drug use during pregnancy.

A more recent population based study of 528,398 singleton births between 2001 and 2003 [27] reported 1.66 (95% CI: 1.16–2.38), 2.08 (95% CI: 1.53–2.83) and 1.47 (95% CI: 1.14–1.91) times higher adjusted odds of LBW, preterm and small for gestational age births, respectively for women with BD, compared with their counterparts with no history of mental illness.

In Sweden, giving birth to preterm, small or growth-retarded babies was found to be elevated even after adjusting for smoking in mothers with affective psychosis (n = 5618) in comparison with 46,246 births to unaffected mothers within a cohort of 1,558,071 singleton births between 1983 and 1997. The risks were greatest in mothers receiving hospital treatment for affective disorder during pregnancy [36].

Unhealthy lifestyle characterized by poor diet, a lack of exercise, obesity and lack of adequate social support are proposed to be associated with the increased risk of adverse pregnancy outcomes in women with affective disorder [35]. However, studies on pregnancy outcomes in BD, where findings were adjusted for socioeconomic factors, parity, maternal age and maternal physical

illness, the relationship between increased risk of adverse pregnancy outcomes and the illness still persisted. This represents a more illness-centered mechanism in explaining the adverse pregnancy outcomes among women with BD.

However the fact that these studies lack information on the medication status of the patients, one should be reluctant to attribute the adverse pregnancy outcome solely to the illness before considering the potential adverse effects of the medications used during pregnancy.

A recent study [24] reported increased risks of cesarean, instrumental and preterm delivery, and nonspontaneous start to delivery in both treated (n = 320) and untreated (n = 554) women with BD in comparison with all other women giving birth (n = 331,263) in the same 4.5-year period as the patients. Microcephaly and neonatal hypoglycemia were more prevalent in infants of women with untreated BD. Being untreated increased risks of women having a small for gestational age infant for weight, length and head circumference. However, the potential role of psychosocial and medical conditions on the growth of infant could not be ruled out. Previously suggested association between lifestyle factors and restriction in the fetal growth did not exist among the treated women. The authors suggested that the drugs used to treat patients, which included antipsychotics (40% of the treated group), valproate (12% of the treated group) and lithium (39% of the treated group), might have masked growth restriction by enhancing fetal growth. Previously, atypical antipsychotics were associated with having large for gestational age infants [37]. However, findings related to lithium use and fetal growth are contradictory [38,39] and valproate has been associated with retardation in fetal growth [40]. Treatment was defined as having filled a prescription for mood stabilizers (lithium, antipsychotics or anticonvulsants) during pregnancy, which does not necessarily imply the use of a drug and causes vagueness in distinguishing treated and untreated groups, thus leaving the effect of medication uncertain.

A large population-based study of deliveries was conducted in Israel that compared women with and without mental disorders [41]. Out of 181,479 deliveries, 607 (0.3%) women reported mental disorder: depressive and anxiety disorders (39%), schizophrenia (11%) or other psychiatric illness (50%). Multivariable logistic regression models determined that psychiatric illness during pregnancy is a risk factor for perinatal mortality and congenital malformations. In this study, BD was not treated separately and possible effects of medication were not excluded.

In summary, data on the pregnancy complications is markedly limited. Findings from a limited number of studies with regard to birth outcome point at an increased risk for having small for gestational age/LBW and preterm births in women with BD. The risk is somewhat affected by the symptom severity. However, the findings are inconclusive since the potential role of confounding factors, such as lifestyle (e.g., smoking and nutrition) and medication use have not been successfully eliminated in the presented studies.

■ Course of illness during pregnancy & postpartum

Pregnancy and postpartum are the two important reproductive periods with regard to the illness course and treatment challenges in women with BD. Owing to variations in study designs and the paucity of data, it is difficult to delineate the sole impact of pregnancy on the course of illness. Recurrence rates vary between retrospective [20,30,32,42–45] and prospective [34,46] studies. It was once suggested that pregnancy exerts a protective effect on the course of illness [30]. This study retrospectively analyzed data of 28 women who had their pregnancies (a total of 56) after the onset of affective disorder but before the initiation of systematic lithium prophylaxis. Later on, these women had been fully stabilized on lithium monotherapy for many years. The patients experienced only a quarter of the expected number of episodes and an eighth of the expected length of episodes during pregnancy. The patients presented significantly higher number and longer lasting postpartum episodes compared with both pre-pregnancy and pregnancy periods. The number of episodes was significantly lower and the duration of episodes was significantly shorter during pregnancy compared with the 9-month pre-pregnancy period. Owing to the fact that all patients discontinued medication long before pregnancy and that none of the pregnant women had ever been on lithium, findings may rule out the adverse effect of medication discontinuation on the recurrences. However, including only a homogeneous group of lithium prophylaxis responders and the small sample size limits the generalizability of the findings.

A contradictory finding comes from another retrospective study where 50 women with BD I

disorder were studied [20]. 50% of women with children (n = 30), 27 of whom were not on psychotrops before, during or soon after delivery, experienced more symptoms of BD during pregnancy than before pregnancy. The worsening of mood, in particular depressive symptoms, increased the risk of having a postpartum mood episode that was almost exclusively depressive, 67% of women with pregnancies experienced a postpartum mood episode within the first month of childbirth. Having a postpartum episode after the first pregnancy predicted a mood episode during the subsequent pregnancy. However, those who did not experience a postpartum episode were still at a high risk for having a mood episode during later pregnancies

In line with the above study, nearly 50% of 186 women with BD I, from the National Institute of Mental Health Genetics Initiative [42] experienced severe emotional disturbances in relation to childbearing. Almost a third of episodes were reported to occur during pregnancy. Similarly, data on 3017 live births from 1212 women with BD I and II disorder in an investigation on the genetic and nongenetic determinants of major affective disorders showed 50 and 40% risk of a perinatal major affective episode per pregnancy/postpartum period in women with BD I and II disorder, respectively. Mood episodes were significantly more common in the postpartum period in BD I [43].

Another study where retrospective data was analyzed revealed at least one mood episode during pregnancy or within 1 month after childbirth in 32% of 252 pregnancies and childbirths of 72 women with BD who were not on lithium maintenance treatment during pregnancy [44]. Early age of illness onset, having mood episode during the first pregnancy and experiencing physical problems during pregnancy were reported to be the predictors of a mood episode during the first postpartum period.

A recent study with a large sample size of 2252 pregnancies of 1162 women with DSM-IV BD I and II disorders or recurrent major depressive disorder reported higher rates of mood, mainly depressive episodes, during postpartum (52%) and during pregnancy (23%) in women with BD compared with women with recurrent major depressive disorder (30 and 4.6%, respectively) [45]. In general, episodes were 3.5-times more prevalent during the postpartum period than during pregnancy, and the risk was consistently higher with BD. A younger age of illness onset, having previous postpartum episodes, fewer years of illness, BD, fewer children and not being married were associated with affective episodes in pregnancy.

Effect of treatment discontinuation on the illness course during pregnancy in women with BD is another important issue. The first systematic study addressing the impact of lithium discontinuation retrospectively compared the recurrence rates of episodes in 101 women with DSM-IV BD I and II during pregnancy and postpartum (n = 42) with that of 59 age-matched nonpregnant women during equivalent periods (weeks 1–40 and 41–64) for after either rapid (1–14 days) or gradual (15–30 days) discontinuation of lithium [32]. Both pregnant and nonpregnant women showed similarly high (~50%) rates of recurrence during the first 40 weeks of lithium discontinuation. The rate was markedly higher compared with the year before going off lithium (21%). Postpartum period posed a 2.9-times higher risk (70%) for recurrences even in those who did not relapse during pregnancy compared with the nonpregnant women during the same period (24%). Most importantly, recurrence risk was greater after rapid than after gradual discontinuation. Recurrence rates did not differ between BD I and II patients but it was higher in patients with more previous affective episodes. Pregnant women were found to experience more depressive or dysphoric-mixed episodes (63% than nonpregnant women 38%).

We have detected two prospective studies [34,46] where rates and polarity of recurrences, as well as time to recurrence, were assessed throughout pregnancy in women who continued versus discontinued medication. In the first observational clinical cohort study [34] pregnant women with DSM-IV BD I or II (n = 89) who were euthymic at the time of conception were included. In total 62 discontinued their medication at most 6 months prior to conception. Rapid versus gradual discontinuation was evaluated as a risk factor for recurrence rate and time to recurrence. Results revealed an overall 71% risk of at least one recurrence in pregnancy. Recurrence risk was twofold higher, and the proportion of weeks spent ill during pregnancy was five-times greater in women who discontinued medication rapidly compared with those with gradual discontinuation. Median recurrence latency was 11-times shorter after abrupt/rapid compared with gradual discontinuation of mood stabilizer. Similar to the previous retrospective

study [32], most recurrences were depressive or mixed, and previous higher episode frequency posed a risk factor for recurrence during pregnancy. In contrast to the above study, having BD II was among the predictors for illness recurrence together with earlier age of onset of illness, antidepressant use and being on anticonvulsants instead of lithium.

In the other prospective study 26 initially clinically stable pregnant women diagnosed with DSM-IV BD I, II or not otherwise specified (NOS) who continued lamotrigine treatment (n = 10) to those who discontinued (n = 16, with 14 rapid discontinuation) all mood stabilizers throughout pregnancy were compared [46]. Discontinuation within 1–13 days was considered as rapid discontinuation. Results demonstrated a 100% recurrence rate of a new episode after discontinuing medication as opposed to 30% recurrence rate in those who continued lamotrigine. Time to recurrence was 12.1-times shorter in the discontinuation group than in the lamotrigine-treated group.

In a recent review, Sharma and Pope pointed out three research-based sources for the finding of a positive effect of pregnancy on BD: nonclinical samples in which the population presented uniformly low rates of BD during pregnancy; clinical studies where pregnant women did not use psychotropic medications or the rate of use such medications was low; large cohort studies that reported reduced rates of psychiatric hospitalization [47]. The authors indicated that the prospective studies included patients who were on psychotropic medications including antidepressants and stressed the possible negative impact of increased rates of antidepressant use in recent cohorts. The absence of prospective studies, focusing on unmedicated pregnant women with BD, was considered to be a limiting factor to assess the effect of pregnancy on the natural course of illness. They also draw attention to the design issue in some studies that reported negative effect of pregnancy where the primary aim was to assess the impact of mood stabilizer discontinuation rather than to assess the effect of pregnancy on BD.

In summary, despite an earlier finding on the protective effect of pregnancy in BD [30], later retrospective and prospective studies repeatedly showed high rates of recurrences during pregnancy and particularly postpartum period in women with BD. Owing to lack of control groups (i.e., nonpregnant women being followed during the same study periods or absence of prepregnancy vs pregnancy comparisons) in some studies it is not possible to attribute the recurrences to pregnancy solely [42–45]. In line with this is the finding of similar but high recurrence rates in both pregnant and nonpregnant women after lithium discontinuation [32]. However, women with BD seem to experience markedly higher recurrences during pregnancy compared with women with recurrent major depression. However, the increased risk of illness recurrence during postpartum period is evident [20,32,42–44]. Most importantly, findings clearly show the adverse effect of medication discontinuation, particularly abrupt discontinuation on the illness recurrence [32,34,46]. Therefore, it is wise to consider the high risk of recurrence and morbidity associated with discontinuing maintenance mood stabilizer treatment versus the risks of fetal exposure to mood stabilizers.

Postpartum as a risk for misdiagnosis

It is not uncommon that women fail to report symptoms of an elevated episode unless questioned specifically and tend to highlight symptoms of depression during postpartum. Thus, misdiagnosis of BD II as major depressive disorder in this period is a serious risk [48]. It is crucial that the appropriate measures such as screening for BD, particularly type II, are taken for all women under antenatal care. Unfortunately, currently, no specific screening instruments for bipolarity have been designed to be used before or after delivery. The Edinburgh Postnatal Depression Scale [49] and the Postpartum Depression Screening Scale [50] are the two most frequently used screening instruments. However, neither has been validated in women with BD. The Mood Disorders Questionnaire (MDQ) has been suggested to be a promising tool for screening BD during pregnancy and postpartum because data retrieved using the MDQ in perinatal population already exists; the MDQ is available for use in the primary care setting; it covers symptoms of bipolarity in a wide range including irritability and impulsive behavior; it is readily available in several languages; and some scoring adjustments can increase its sensitivity for BD II and BDNOS [51]. The clinician can also pursue an accurate diagnosis for postpartum bipolarity by following some clues such as occurrence of hypomania during postpartum, appearance of depression immediately after delivery, atypical features, racing thoughts

and co-occurring psychosis during depression, family history for BD, antidepressant-related response challenges (rapid response, poor response and manic switch), and the presence of mixed features in the depressive episodes [48].

Another diagnostically important point is related to the postpartum psychosis for which the rate was shown to be 26% in 313 deliveries of 152 parous women with BD. The rate of puerperal psychosis in women with BD with a family history for puerperal psychosis (74%) exceeded substantially, the rate of puerperal psychosis in those without such family history (30%) indicating a familiarity in the condition [52].

■ Treatment considerations during pregnancy

Women of childbearing age with severe mental disorders are substantially exposed to psychotropic drugs. In a recent epidemiological study, 74.8% of all women of childbearing age with schizophrenia and 80.1% of all women of childbearing age with BD were shown to have exposed to antipsychotic drugs or mood stabilizers during a 12-month period [53]. Owing to the time gap between conception and the recognition of the pregnancy, offspring of women with such psychiatric disorders as BD are exposed to medication during the first 3 months of gestation when the treatment-related malformations mostly occur. Therefore, it is clinically important to understand ramifications of such medication exposure. Data on lithium, anticonvulsant mood stabilizers antipsychotics and antidepressants are given below.

Lithium

A recent systematic review on lithium [54] identified 1756 cases of exposure to lithium during early pregnancy both in case reports and in studies with varying methodological designs. The review focused on the potential relationship between *in utero* exposure to lithium, which had begun within the end of the first trimester, and perinatal complications. Based on data from prospectively followed 371 cases of lithium exposure during early or throughout pregnancy, the incidence of neural tube defects are reported to be as high as 13.4 per 1000 live births. The figure is higher than the peak of incidence seen in the unexposed population. However, this may well be a random cluster; therefore, the reviewers suggested that this may indicate a potential increase in the risk of neural tube effects. The early reports generated from the register of the lithium babies had alarmed for approximately 400 times increase in the rate of the Ebstein's anomaly in infants exposed to lithium *in utero* compared with unexposed infants [55]. A later re-evaluation of the risk associated with *in utero* exposure to lithium found the incidence of this cardiac malformation in lithium-exposed infants to be only 10–20 times (1–2/1000 live births) higher than that appreciable in the general population [56]. This is a very low risk, meaning that the absolute risk of lithium causing the defect is approximately one in 2000. However, pooled data from prospective studies came up with an intermediate incidence of 10.78/1000 live births [54]. Perinatally, lithium-exposed fetuses are more often premature and large for gestational age, and can experience neonatal toxicity of hypothyroidism, nephrogenic diabetes insipidus and 'floppy baby' syndrome (i.e., cyanosis and hypotonia). Perinatal complications were shown to be associated with the lithium levels in the newborn's serum, particularly for concentrations above >0.64 mEq/l [57]. In a small longitudinal study infants exposed to lithium *in utero* did not show adverse effects on growth, neurologic, cognitive, and behavioral development up to 15 years old [58].

Use of lithium during pregnancy should target the lowest effective dose, which can maintain maternal serum levels 16–18 weeks of gestational age due to concern for cardiac malformations associated with lithium exposure in the first trimester. Lithium levels should be monitored closely, as vomiting in early pregnancy and increased renal excretion in later pregnancy can affect levels [54,59]. After delivery, it is recommended to assess cord blood lithium levels, neonatal thyroid and kidney functions, particularly in infants with clinical symptoms of 'floppy baby' syndrome [25].

Anticonvulsant mood stabilizers

A recent systematic review identified more than 20 studies for the commonly used antiepileptic mood stabilizers, sodium valproate, carbamazepine and lamotrigine [60]. The findings defined a degree of consistency in spite of variations in methodology and in the definition of malformation used across the studies. All studies were in women with epilepsy, although some included women treated for other indications. There was a consistent finding of higher malformation rate with sodium valproate than

with either carbamazepine or lamotrigine with a dose-dependent increase in the risk of malformation for valproate in some studies. Overall major malformation rates of 2.9% for carbamazepine, 8.7% for sodium valproate and 2.7% for lamotrigineare reported in the review [60]. However, caution should be taken while interpreting these figures as they do not give comparisons with the figures in the general population. In the ten prospective studies included in this review a significant and replicated association was found between carbamazepine and reduced head circumference as well as for lower birth weight and length. A significant association was found between sodium valproate and neonatal hypoglycemia, with weaker findings for hepatic dysfunction, withdrawal symptoms and reduced birth dimensions. A number of retrospective and prospective studies demonstrated that exposure to valproate in pregnancy is associated with approximately threefold increase in the rate of major anomalies mainly neural tube defects (incidence: 1–2%, mainly spina bifida and only rarely anencephaly), hypospadias, cardiac, craniofacial, skeletal and limb defects and a possible set of dysmorphic features, the 'valproate syndrome' with decreased intrauterine growth [60,61].

With regard to the developmental problems with anticonvulsant mood stabilizers, the reviewers identified nine prospective, and three retrospective cohort studies from 2004 onwards, 11 of which examined the effect of sodium valproate on child development. Despite methodological diversity, an association between valproate exposure during pregnancy and poorer developmental outcomes ranging from a global reduction in IQ to adversities in more specific domains, such as verbal IQ, memory and attention problems, were demonstrated. None of the studies found an association with carbamazepine and poorer developmental outcomes. Only one study included lamotrigine, and no effect on development was found [60]. A recent prospective, observational, multicenter study, which included pregnant women with epilepsy on antiepileptic drug monotherapy (carbamazepine, lamotrigine, phenytoin or valproate), reported dose-dependent associations between fetal valproate exposure and reduced cognitive abilities in various domains at 6 years of age [62].

Studies which examined a dose effect and polypharmacy of antiepileptics found both doses of sodium valproate over 1000 g and polypharmacy associated with later poorer neurodevelopmental outcomes [63].

Owing to the valproate exposure related adversities, it is recommended that valproate should be avoided in pregnancy. There is usually a time lag between conception and recognition of pregnancy, therefore, it may be too late to stop the medication when pregnancy is first diagnosed. Valproate-treated women of childbearing age are to be advised to use contraceptives and stop the medication before any planned pregnancy as neural tube defects are induced in the third week postfertilization. The American Academy of Neurology (AAN) recommends avoidance of valproate during pregnancy [64]. According to AAN, valproate should be used only when clinical circumstances dictate no other treatment alternative. Under such circumstances, preconceptional folic acid at 0.4 g/day or more is recommended to prevent major congenital malformations. Another recommendation is the early assessment for neural tube defects. In addition, it is suggested that the use of the lowest possible daily dose divided into three doses to minimize fluctuations of serum levels of valproate may reduce the risk to the fetus [40].

Most experts are not in favor of using carbamazepine during pregnancy with the exception that no other option is possible [25]. Monitoring of carbamazepine levels in pregnancy is recommended. Evidence to recommend prenatal vitamin K supplementation for reducing hemorrhagic complications was found insufficient by AAN [59]. Pregnancy registries have consistently demonstrated lamotrigine to be a low-risk medication for a developing fetus, both in terms of fetal malformations and postpartum cognitive development, providing an alternative in pregnancy [65]. Some preliminary studies showed a relationship between lamotrigine exposure and orofacial clefts; however, there is no specific evidence of an increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine [66]. When used in pregnancy, due to increased clearance in the last trimester, it is advised to consider increasing the dose for prophylactic purposes. Checking blood levels, is warranted during the second and third trimesters.

First-generation antipsychotics

Owing to decades of usage, first-generation antipsychotics present with one of the largest safety databases available among all psychotropic medications. They do not seem to have

any significant adverse effect either on organogenesis, or neurodevelopment. Their use is suggested as an alternative to mood stabilizers either during the first trimester or throughout the entire pregnancy [25].

Atypical antipsychotics

Atypical antipsychotics have been used widely by women of reproductive age for almost two decades. However, reliable safety data are still limited. Despite small number of studies, including recent larger cohort studies evidence does not indicate an increased risk for major malformations in atypical antipsychotic (olanzapine, risperidone, quetiapine and clozapine) exposed infants [59,67–69]. Data from the Swedish Medical Birth Register report an overall major malformation rate of 4.1% in 147 infants who were exposed to atypical antipsychotics *in utero*. The rate for each specific medication was as follows: clozapine: 5.6%; olanzapine: 3.8%; quetiapine: 0.0%; and risperidone: 3.9% [70]. Although recent data suggest adverse long-term neurobehavioral effects associated with atypical antipsychotic use in pregnancy [71,72], information on neurodevelopmental outcomes is still lacking. Overall, perinatal exposure to atypical antipsychotics is known to alter the birth weight of newborns and may increase the risk for gestational diabetes and for cesarean delivery [67].

Based upon limited data, those pregnant women who use atypical antipsychotics should be monitored closely for weight gain and gestational diabetes. In addition, the growth rate of their fetus should be watched closely. Although replacing the ongoing atypical antipsychotic treatment with a better characterized typical antipsychotic may be an option for safety reasons, the benefit–risk weighing is recommended in patients who have been benefiting from preventive effects of atypical antipsychotics.

Antidepressants

Antidepressants, especially specific serotonin reuptake inhibitors are widely used in mood disorders. However they are always recommended to be used in combination with mood stabilizers in BD [73,102]. Although polypharmacy is known to have a more complex effect on the offspring compared with monotherapy [63], it is still worth knowing the potential effects of antidepressants as a class on the devoloping fetus.

In a recent study with a large sample size (n = 7696), prenatal selective serotonin reuptake inhibitor (SSRI) use was associated with reduced fetal head growth but was not associated with reduced body growth. The SSRI-exposed children were at higher risk for preterm birth. The clinical importance of these findings are yet to be explored [74].

Earlier highly powered case–control studies showed a link between SSRIs and specific congenital malformations [75,76]. However, the caveats that the specific defects implicated are rare and the reported absolute risks in both studies were small should be taken into consideration. A recent meta-analysis showed an increased odds of developing major congenital malformations in children exposed to SSRI medications *in utero*. The increase in risk was driven mainly by paroxetine and fluoxetine. The link between fluoxetine and cardiac malformations is still uncertain. Citalopram and sertraline had a nonsignificant impact on effect size. SSRIs as a medication class were not significantly associated with increased risk of either minor congenital malformations or cardiac malformation in infants exposed. However, subgroup analysis of individual agents indicated that paroxetine was associated with increased odds of cardiac malformation [77]. A recent population-based, case–control study in the USA [78] suggests a probable association between maternal periconceptional use of venlafaxine and certain birth defects, including cardiovascular system anomalies. However, the estimates are not precise and the confidence intervals are wide due to the small number of venlafaxine-exposed mothers during early pregnancy who have been included in the analysis. The investigators stress on the need for additional confirmatory studies. In addition to this, no particular reference for bipolar depression was made in the study.

■ General treatment considerations for maintenance & prevention during pregnancy & postpartum

A close monitoring of mood and sleep, particularly during postpartum is necessary as sleep deprivation can have deleterious effects on the mood. Adjunctive treatment can be considered to correct postpartum sleep disturbance. Sleep hygiene should be carefully considered against the benefits of breastfeeding. During pregnancy, risks of medication to the fetus versus the risks of leaving the illness untreated should be balanced. When treatment is necessary, using medications as monotherapy at minimal effective doses is

preferable. Antidepressants are to be carefully used in the case of depression to prevent switching to hypomania. Medications with potential efficacy in preventing postpartum mood episodes can be chosen to treat depression during pregnancy [48].

Conclusion & future perspective

The approach to pregnancy and postpartum in women with BD, has been changing over the past decades. First, women with BD were advised to avoid pregnancy. With the discovery of lithium and its teratogenic properties, women were advised to stop lithium, particularly during the first trimester, and continue using it towards the end of pregnancy. Current knowledge on the increased risk for a more morbid course of illness after discontinuing medication, in particular lithium during pregnancy coupled with the repeatedly reported high recurrence rates during postpartum requires that the pregnancy should be conceptualized as an event that needs to be managed along with the treatment course. Currently, based on limited data on the effects of various medications on the developing fetus, it does not seem to be possible to make distinctive statements on the medication selection particularly with regard to various atypical antipsychotics and antidepressants. However, based on teratogeneity data, there are warnings to avoid certain medications (i.e., valproate) during pregnancy.

The effect of BD on birth outcome is vague given the confounding effects of several lifestyle-related factors and medication use. More systematically collected data with a more elaborate statistical approach is needed in order to delineate medico-psycho-social factors from the impact of illness on the development of the offspring.

Similarly the sole effect of BD and its subtypes on the course of illness during pregnancy is still to be explored given that the present data areconfounded by either medication use or medication discontinuation. Even in the presence of a homogeneous group with no prior maintenance treatment [30], the sample size is too small, limiting the generalizability of the findings. The number of BD II patients are too limited to reach a distinctive conclusion on the effect of bipolar subtype on the recurrences during pregnancy and postpartum. Data are lacking on the occurrence of a first mood episode during pregnancy and its conversion to BD. However, to date, no study has reported comorbid psychiatric conditions and their effect on the pregnancy in BD.

Planning and managing pregnancy and later on postpartum in BD is a challenging task both for the clinician and for the patient. Patients need the assistance of an expert while planning the pregnancy as there are several educational points related not only to pharmacotherapy, but also to the neurobiology of illness, such as the importance of sleep hygiene before, during and after pregnancy.

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