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## Mood stabilizers in pregnancy and lactation

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### Abstract

Management of bipolar during pregnancy and postpartum is very challenging. The treating clinicians have to take into account various factors like current mental state, longitudinal history of the patient, past history of relapse while off medication, response to medication, time of pregnancy at which patient presents to the clinician, etc. The choice of drug should depend on the balance between safety and efficacy profile. Whenever patient is on psychotropic medication, close and intensive monitoring should be done. Among the various mood stabilizers, use of lithium during the second and third trimester appears to be safe. Use of valproate during first trimester is associated with major malformation and long-term sequelae in the form of developmental delay, lower intelligence quotient, and higher risk of development of autism spectrum disorder. Similarly use of carbamazepine in first trimester is associated with higher risk of major congenital malformation and its use in first trimester is contraindicated. Data for lamotrigine (LTG) appears to be more favorable than other antiepileptics. During lactation, use of valproate and LTG is reported to be safe. Use of typical and/atypical antipsychotic is a good option during pregnancy in women with bipolar disorder.

**Keywords:** Antipsychotics, bipolar disorder, mood stabilizers, pregnancy

### INTRODUCTION

Mood stabilizer is the term used for the agents which are useful in the treatment of bipolar disorders. However, the definition of this class of drugs is not yet settled. Some researchers/clinicians restrict the use the term mood stabilizer for agents, which have efficacy in reducing the frequency or severity of various type of episodes in bipolar disorder without worsening the frequency or severity of other types of episodes. [1,2,3] Accordingly, antidepressants, which can induce manic switch and typical antipsychotics, which are shown to worsen depressive symptoms would not classify as mood stabilizers. On the other hand, some authors defined mood stabilizers as agents that have efficacy in treating both manic and depressive symptoms.[4] Bauer and Mitchner[5] expanded this definition and defined mood stabilizer as an agent, which has efficacy in treatment of acute manic symptoms, acute depressive symptoms and can prevent development of manic and depressive symptoms.[5]

Although the definition is not settled, mood stabilizers are commonly understood as agents that are useful for treatment of acute episodes (manic or depressive) and prevention of relapse or recurrence of symptoms,

without worsening of symptoms of either polarity. In recent times, many drugs have been evaluated as mood stabilizers. The term mood stabilizers is mostly used in relation to lithium, anticonvulsants like valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin etc., and atypical antipsychotic like olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Some other drugs like clonazepam, calcium channel blockers etc., have also been evaluated as mood stabilizers. In this paper, the authors would limit to use of lithium, anticonvulsants, atypical antipsychotic and benzodiazepines in subjects with bipolar disorders.

## **BIPOLAR DISORDER: RISK OF RECURRENCE DURING PREGNANCY AND POSTPARTUM**

Bipolar disorder is considered a severe mental disorder that usually starts in late teens and early twenties and is characterized by episodes of mania, depression, hypomania and mixed episodes. The disorder has equal prevalence in both genders. Women are exposed to the risk of an episode throughout their reproductive life because of its age of onset.[6] The decision to stop drugs when women with bipolar disorder become pregnant or plan to conceive is difficult. The treating psychiatrists of such patients face the challenge of having to minimize the risk to the fetus, while at the same time, limiting the impact of maternal morbidity. Patients and their clinicians also face the reality that decisions either to use or not to use psychotropic medications can be associated with complications. Hence, concluding as to what constitutes a reasonable risk during pregnancy requires shared responsibility, but the ultimate decision rests with the informed patient.

Studies have shown that female patients with bipolar disorder are at high risk of relapse of symptoms during the pregnancy[7,8,9] and early postpartum period.[10,11,12,13] The risk of relapse during pregnancy has been estimated to be 50% or more,[7,8,9] with recurrence risk reported to be 2.3 times higher after discontinuation of mood stabilizer. In a prospective study, it was found that women who discontinued the mood stabilizer spent about 40% of the time of pregnancy in episodes compared to 8.8% of time spent by those who continued mood stabilizer. It was also evident that the recurrence risk was higher and earlier after rapid discontinuation of mood stabilizer. The authors also found that women, who had younger age of onset, longer duration of illness, more number of previous episodes, history of rapid cycling, suicide attempts, associated comorbid disorders and antidepressant use, had higher chance of recurrence during the pregnancy. Treatment discontinuation and antidepressant use remained as independent risk factors even after adjusting for other risk factors.[9]

With regard to the postpartum risk, studies have shown that 40–70% of untreated bipolar women may experience postpartum episode.[14] It is also known that the risk of postpartum relapse is high in those who discontinue prophylactic treatment.[13]

## **POTENTIAL RISKS OF PHARMACOTHERAPY IN PREGNANCY IN BIPOLAR DISORDERS**

For obvious ethical reasons, it is not possible to conduct randomized placebo controlled studies on medication safety in pregnant and lactating women. Most of the information about the reproductive safety of drugs is derived from case reports, case series, and retrospective studies. Very few studies involve prospective design. Hence, knowledge regarding the risks of prenatal exposure to psychotropic medications remains far from complete. It is evident that all psychotropic medications diffuse across the placenta, which exposes the fetus to some degree of risk.[15] In the past, the effects of psychopharmacological therapies was exclusively discussed in the context of their risk during the first trimester when organ formation occurs, it is now recognized that psychotropics are harmful even after organogenesis, as intrauterine exposure during the second and third trimester can lead to postnatal complications.[16] Accordingly, the impact of psychotropic drugs on the fetus and new born has been studied in the form of teratogenicity (risk of congenital physical deformities over the base line rate of 2.0–

2.5%), obstetrical complications (preterm delivery, low birth weight, low Apgar scores necessitating intensive care), perinatal syndrome (physical and behavioral symptoms noticed shortly after birth) and long-term behavioral sequelae (neurobehavioral abnormalities in children), including long-term neurobehavioral abnormalities in children who were exposed to psychotropics in utero.[15]

## REPRODUCTIVE SAFETY OF MOOD STABILIZERS

No psychotropic drug has been approved by the US Food and Drug Administration (FDA) for use during pregnancy. FDA has established a classificatory system for medications based on data derived from human and animal studies.[17,18] According to the risk, medications are classified into 5 risk categories (A, B, C, D, and X). Medications placed in category “A” are considered safe for use during pregnancy, however, no psychotropic medication is classified as belonging to category “A.” Medications placed in category X are contraindicated due to demonstrated fetal risks, which outweigh benefit to the patient. Drugs in categories B to D are considered to have intermediate risks, which are greatest in category D. Most antipsychotics are classified as category C agents for which adequate human studies are lacking and fetal effects are seen in animal studies or those in which the animal studies are also insufficient; making it difficult to rule out the fetal risks. Mood stabilizers like lithium, valproate and carbamazepine are classified as category “D” drugs.[15,17,18] It is important to remember that this classification is not adequate for making all decisions and the psychiatrists have to rely on other sources of information when recommending the use of psychotropic medications during pregnancy.[19,20]

## MOOD STABILIZERS AND LACTATION

Breast milk is considered as an ideal form of nutrition and is known to confer many advantages to the new born and the infant. In addition, breast feeding is also known to confer health benefits to mother. As per the American Academy of Pediatrics,[21] human milk is known to reduce the incidence and/or severity of a wide range of infectious diseases including bacterial meningitis, bacteremia, diarrhea, necrotizing enterocolitis, otitis media, respiratory tract infection, urinary tract infection, and late-onset sepsis in preterm infants. In addition, breast feeding is also reported to be associated with reduced postneonatal infant mortality rates, decreased rates of sudden infant death syndrome in the 1<sup>st</sup> year of life, lower incidence of type 1 and type 2 diabetes mellitus, Hodgkin disease, lymphoma, leukemia, overweight and obesity, hypercholesterolemia and asthma in older children and adults. Further, it is suggested that breastfeeding is associated with slightly enhanced performance on tests of cognitive development. Breast feeding is also very important for development of emotional bond and attachment between the mother and the infant.[22,23] It is also known that continuation of breast feeding decreases postpartum bleeding and leads to more rapid uterine involution, decreased menstrual blood loss, increased child spacing by lactational amenorrhea, earlier return to prepregnancy weight, decreased risk of breast and ovarian cancer, and possibly decreased risk of hip fractures and osteoporosis in the postmenopausal period.[24]

Hence, asking the women not to feed the baby can lead to an ethical dilemma. The decision regarding continuing or not continuing breast feeding while continuing mood stabilizers is a difficult one. Ideally, a risk benefit analysis should be carried out taking into consideration the physiological and psychological benefits of breastfeeding; the potential adverse effect of untreated maternal mental illness on the infant and maternal child bonding; impact of psychotropic medication on the cognitive and behavioral development of the infant, and the consequences of untreated mental illness on the mother.[24] If a decision is taken to allow continuation of breast feeding, it is important for the clinicians to have basic knowledge about the physiological aspects of milk secretion and the physiological maturation of the newborn child. The exposure of infant to various medications is dependent on the rate of absorption into maternal circulation, diffusion from maternal circulation to breast milk, and absorption of the agent in the infant. The

concentration of medications in breast milk is influenced by lactose, serum albumin, lysozyme and approximately 30 other enzymes, prolactin, and minerals like calcium and phosphates. It is known that, compared with the fore milk (the milk ejected during the first half of a feeding), hind milk (the milk ejected during the second half of a feeding) has higher lipid content; hence, the milk secreted in the second half will have a higher concentration of lipid soluble maternal psychotropic medications than the first half. [25] In terms of physiological maturation of the neonate, it is important to remember that the amount of neonatal cytochrome P-450 activity is about half that found in adults. Ability to conjugate various compounds develops from minimal levels to almost adult levels within 2 weeks of birth in most cases. [26] Further, compared to adults, kidneys of newborn are functionally immature; hence the psychotropic medications that are predominately eliminated through kidney may accumulate. Compared with adults, the blood brain barrier in newborn is also immature, hence the lipid soluble agents can be more concentrated (10–30 times) in the cerebrospinal fluid than in serum and may be higher in infants for a given plasma concentration. In addition, compared to older infants, neonate have relatively lower fat storage sites, accordingly central nervous system (CNS) concentrations of lipid soluble substances are greater in newborns. [25]

## EFFECTS OF PSYCHOTROPICS: PREGNANCY AND LACTATION

### Lithium

Use of lithium in pregnancy has been a cause of concern since the beginning because of the risk for major congenital anomalies with prenatal exposure to lithium, especially cardiovascular malformations such as Ebstein's anomaly. [27,28,29] As per the initial estimations, the risk for Ebstein's anomaly in infants with first trimester lithium was 400 times more than the background baseline rates. [27,28,29,30] Cohen *et al.* [30] carried out a metaanalysis and calculated the risk for Ebstein's anomaly, with first trimester exposure to lithium, to be between 1/1000 (0.1%) and 1/2000 (0.05%) births. [30] This risk was 10–20 times higher than the risk of Ebstein's anomaly in the general population. It is important to understand that the absolute risk is small (0.05–0.1%), and lithium is considered to be the safest mood stabilizer for use during pregnancy. [30] Some of the recent studies suggest increased risk of miscarriage. [31] In addition, use of lithium has been associated with congenital abnormalities like large for gestational age infants, [32] anencephaly, [33] oromandibular-limb hypogenesis [34] and premature closure of arterial duct. [35] Exposure to lithium during labor and delivery is associated with the risk of “floppy baby” syndrome, which is characterized by muscular hypotonia with impaired breathing and cyanosis in new born. [36,37,38] Apart from this, there are occasional reports of neonatal hypothyroidism, nephrogenic diabetes insipidus, and polyhydramnios. [15,38,39]

Some groups recommend discontinuation of lithium several days or weeks prior to delivery to minimize the risk of neonatal toxicity. [31,37,39,40] Newport *et al.* [41] evaluated the distribution of lithium concentration in umbilical cord blood to maternal blood and reported that lithium concentration was uniform (umbilical cord blood: Maternal blood ratio = 1.05; standard deviation = 0.13) across a wide range of maternal lithium concentrations (0.2–2.6 mEq/L). In the same study, higher lithium concentrations (>0.64 mEq/L) at delivery were associated with significantly lower Apgar scores, higher rates of CNS and neuromuscular complications in infants and resultant longer duration of hospital stay. It was observed that withholding lithium therapy for 24–48 h before delivery resulted in reduction in maternal lithium concentration by 0.28 mEq/L, which the authors considered could lead to improvement in obstetrical outcome. A few reports have described adverse effects in the form of lethargy, hypothermia, hypotonia, and T-wave modifications on electrocardiogram (ECG) in newborns of mothers who continued to take lithium during the postpartum period. [32,42,43] In a recent study, the maximum recommended dose of lithium in pregnant women, based on a physiologically based pharmacokinetic model, was estimated and

reported as 400 mg thrice daily.[44] Data are limited with regard to the behavioral outcomes of children exposed to lithium *in utero*. Follow-up studies of children (for 3.5–5 years) exposed to lithium during pregnancy have come up with lack of evidence for significant behavioral problems.[41,45] However, these studies have been limited by small sample size. One of the recent studies evaluated 15 children, exposed to lithium prenatally, at the age of 3–15 years of age and reported lower scores on the performance intelligence quotient (IQ), although overall intelligence was within normal limits. However, no abnormality was observed in growth, behavior and general development.[46]

### Anticonvulsants

Compared to lithium, higher teratogenic risk has been reported to be associated with anticonvulsants. The risk for major birth defects in infants born to women receiving anticonvulsants has been reported to be twice that seen in general population.[47] Further it is seen that the increased risk for teratogenesis is associated with high maternal serum anticonvulsant levels and exposure to multiple anticonvulsants at a time.[48,49]

### Valproate

Valproate is now considered as a mood stabilizer. It is effective in management of acute manic and depressive episodes and is also useful in prevention of relapse of both manic and depressive episodes. Valproic acid and its various derivatives have been known to have an increased risk of causing neural tube defects in the range of 1.0–5.0%, which is about 2–10-fold higher than the general population base rates of about 0.5%.[50,51] These risks are of concern because neural tube formation occurs within the 1<sup>st</sup> month of gestation, a time period during which the pregnancy is not even diagnosed. The neural tube defect with valproate more often involves the lumbosacral rather than the anencephalic region, suggesting the effect of valproate on the closure of neural crest.[52] Prenatal exposure to valproate has been associated cardiovascular malformations, intrauterine growth retardation, genital anomalies, hydrocephalus, limb defects (radial ray effects, fibrous aplasia of lower limbs), and pulmonary atresia.

[47,48,49,50,51,52,53,54,55] In a prospective study, Wyszynski *et al.*,[53] evaluated the rate of occurrence of major malformations at birth in infants of mothers who had taken valproate as monotherapy and had enrolled in the North American Antiepileptic Drug (AED) Pregnancy Registry. Of the 149 valproate monotherapy exposed pregnancies, major malformations were seen in 16 cases. When these data were compared with the major malformations with other anticonvulsants, it was concluded that valproate was associated with more frequent adverse effects. Another recent case–control study, which was based on European Surveillance of Congenital Anomalies antiepileptic-study database, evaluated the outcome of exposure to valproic acid monotherapy in 180 registrations. Compared to no use of antiepileptic medications, use of valproic acid during the first trimester was associated with increased risk of spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyl and craniosynostosis.[56] Emerging data also suggest that the risk of malformations with valproate is dose related[57,58] with higher risk associated with use of valproate in excess of 1000 mg/day.[57] Data based on the review of United Kingdom (UK) and Ireland Epilepsy and Pregnancy Registers have estimated the risk of major congenital malformations with valproate monotherapy to be 6.7%, which is higher than that reported for carbamazepine (2.6%) and lamotrigine (2.3%).[59]

Use of valproate close to delivery is associated with withdrawal symptoms of abnormal tone, feeding difficulties, irritability and jitteriness.[54] In addition, neonatal complications like heart rate decelerations, [60] liver toxicity,[61] hypoglycemia,[62] and reductions in neonatal fibrinogen levels[63] have also been reported. Long-term behavioral and cognitive outcome with exposure to valproate in pregnancy has been evaluated. Meador *et al.*[64] evaluated the IQ scores at the age of 3 years of 258 children who were exposed to anticonvulsants during pregnancy. IQs were lower for those exposed to valproate compared to



carbamazepine, LTG, and phenytoin, after controlling for maternal IQs and blood levels of anticonvulsant medications. It was further found that maternal valproate blood level had significant inverse correlation with cognitive functioning. A follow-up of the children at 4.5 years showed the persistence of lower IQ, which was negatively associated with dose of valproate[65] Subsequently, a large scale study evaluated IQ of children at the age of 6 years and provided credence to this finding.[66]

A study also suggested that compared to the children exposed to carbamazepine and lamotrigine, children exposed to valproate prenatally have lower cognitive fluency and originality.[67] Recent studies have also reported neurodevelopmental delay in children exposed to valproate prenatally.[68,69,70] Another cause of concern is high rate of autism spectrum disorder among the infants prenatally exposed to valproate monotherapy with absolute risk of 4.42% for autism spectrum disorder and 2.5% for childhood autism. [71,72] A recent review of data also suggests increase in the risk of attention deficit hyperkinetic disorder with antenatal exposure of valproate.[73]

With regard to secretion of valproate in breast milk, it has been shown that valproate is minimally present in breast milk. Piontek *et al.*[74] evaluated the level of valproate in 6 breast-fed mother-infant pairs and reported that serum valproate levels in the infants ranged from 0.9% to 2.3% of the mother's serum level. In another study of 2 infants whose breastfeeding mothers were taking valproate, Wisner and Perel[75] reported that valproate concentrations in the infants were 1.5% and 6%, respectively. The American Academy of Neurology and American Academy of Pediatrics support breastfeeding if the mother is taking valproate.[76,77]

### Carbamazepine

Use of carbamazepine during the first trimester of pregnancy has been shown to be associated with the risk of neural tube defects at a rate of about 0.5–1.0%.[78,79] Infants exposed to carbamazepine prenatally are also at increased risk for craniofacial abnormalities, fingernail hypoplasia, developmental delay, growth retardation, microcephaly, spina bifida, and cardiac abnormalities.[47,80] Recent data suggest that the risk increases in a dose-dependent pattern with higher risk with doses 400 mg/day.[81] Transient hepatic toxicity (cholestatic hepatitis and direct hyperbilirubinemia) in neonates exposed to carbamazepine during pregnancy has also been noted.[80,82] In terms of behavioral and cognitive outcome, studies have shown that carbamazepine exposure during pregnancy and neonatal period does not lead to significant cognitive dysfunction in childhood.[83,84]

The data on serum concentrations of carbamazepine among breastfeeding infants are largely based on assessment of newborns of mothers who were on carbamazepine during the pregnancy. Evidence suggests that in general the concentration of carbamazepine in breast milk is much lower than the maternal serum levels, with concentrations in infants ranging from 6% to 65% of maternal levels.[85] Studies that have evaluated carbamazepine exposure in nursing infants have reported occasional cases of transient hepatic dysfunction.[80,82] Both American Academy of Neurology and American Academy of Pediatrics support breastfeeding if the mother is taking carbamazepine.[76,77]

### Oxcarbazepine

Oxcarbazepine, a congener of carbamazepine has been used for the treatment of bipolar disorders. In a review of data, Eisenschenk[86] reported that, in the 248 patients identified in the literature as receiving oxcarbazepine during pregnancy, 6 malformations were reported; indicating a malformation risk of 2.4%, which is within the 2–4% malformation rate seen in the general population. It is noteworthy that in 4, out of the 6 pregnancies with congenital malformation, the mothers were also receiving adjunctive antiepileptics. The malformations reported include major cardiac malformation (adjunctive therapy with phenobarbital), ventricular septal defects (1 monotherapy and 1 adjunctive therapy with lamotrigine),

facial malformations (cleft soft palate, facial dysmorphism, terminal transverse defect, disproportion of head and trunk, and extrophia vesicae) in 1 case, congenital hydronephrosis (adjunctive therapy with vigabatrin), major urinary tract defect (1 case) and 1 case of spina bifida cystica and clubfoot (adjunctive therapy with valproate and clobazam).

### Lamotrigine

In recent time use of lamotrigine in bipolar disorders has increased. However, most of the data about its safety in pregnancy is available from its use in pregnant females with epilepsy. Newport *et al.* [87] pooled the data from the available studies and reported 2.6% risk (78/2974) of major fetal anomalies following first trimester exposure to lamotrigine, which is within the range of anomalies among births reported in the general population. The obstetrical outcome information is maintained by the International lamotrigine Pregnancy Registry. Cunnington *et al.* [88] reported that of the 414 first trimester exposures to lamotrigine monotherapy, about 3% (12 offspring) had major birth defects which are similar to that in general population. However, no distinctive pattern of major birth defects was apparent among the birth defects detected following exposures to lamotrigine monotherapy. They found a higher rate of major birth defects (12.5%) in 88 first trimester exposures to combination of lamotrigine and valproate. Recently, some data have emerged to suggest that exposure to LTG is associated with increase in the risk of oral clefts. Holmes *et al.* [89] presented the data from North American AED Pregnancy Registry with regard to lamotrigine. Of the 684 infants exposed to lamotrigine, 16 (2.3%) had major malformations. Five infants (7.3/1000) had oral clefts (isolated cleft palate [3 cases], isolated cleft lip [1 case], and cleft lip and palate [1 case]). The rate among the lamotrigine-exposed infants was 10.4-fold higher in comparison to unexposed infants ( $n = 206,224$ ) surveyed at birth at Brigham and Women's Hospital in Boston. However, another study based on data from UK Epilepsy and Pregnancy Register, did not confirm this finding. The authors reported data of 1229 pregnancies exposed to lamotrigine as monotherapy, resulting in 1151 live births. Twenty-eight major congenital malformations were reported with no specific pattern; of which only one male infant was born with nonsyndromic cleft lip and palate. [90] Recent data suggest that the risk increases in a dose dependent pattern with higher risk with doses 300 mg/day. [81] Studies in women with bipolar disorder treated with lamotrigine during pregnancy suggest lower serum level to dose ratios during pregnancy than during the postpartum period. [91] Studies also suggest higher clearance level of lamotrigine during pregnancy and suggest the need for dose adjustment. [92] In terms of neurobehavioral effects a follow-up study of 23 infants, reported no neurobehavioral effects with lamotrigine at 12 months of age. [93] However, one recent report suggested behavioral outcomes comparable to valproate. The children had reduced nonverbal IQ scores, along with lower scores on motor and sensory measures, lower scores on executive functions, behavioral measures and attentional measures as per the parent-report. [94]

Few case reports and case series reported mean milk/plasma ratios ranging from 0.40 to 0.61 for lamotrigine. [95,96,97,98,99] One recently published study involving 30 lactating mothers and their infants reported a mean milk/plasma ratio of 41.3% with a range of 5.7–147%. The authors also reported higher lamotrigine concentrations in breast milk 4 h after maternal dose, although this finding was not statistically significant. Compared with maternal plasma concentrations, the plasma concentrations in infants were 18.3%. Based on these findings authors reported infant lamotrigine dose to be 0.51 mg/kg/day, and compared to maternal dose and the relative infant lamotrigine dose was 9.2%. Almost all infants (7 out of 8) were found to have mild thrombocytosis at the time of serum sampling. No other adverse events were observed or reported in the breast-fed infants. [100]

### Topiramate

Animal studies have demonstrated craniofacial and skeletal abnormalities. [101,102] Kwarda *et al.* [103] reported 2 malformations (micrognathia, phimosis) in 29 pregnancies exposed to topiramate monotherapy.

Hunt *et al.* [104] reported pregnancy outcome in patients receiving topiramate based on UK Epilepsy and Pregnancy Register. In the 70 pregnancies exposed to topiramate monotherapy, 3 major malformations were seen; 2 infants had cleft lip and cleft palate and 1 had hypospadias. It was also seen that women who gave birth to neonates with major malformation were receiving relatively higher doses (mean - 400 mg vs. 238 mg) compared to women who gave birth to children without malformation. It was also seen that out of 61 cases exposed to monotherapy and for whom data was available, 6 infants were born at 37 weeks of gestation or less. Further, of the 56 cases exposed to monotherapy and for whom full data on gestational age and birth weight was available, 8 (14.3%) were small for gestational age. However, in women receiving topiramate as part of polypharmacy, 13 major malformations were reported. It was observed that major malformation rates were higher when topiramate was given along with valproate than with other antiepileptics. A large sample study based on the Global Medical Safety database, reported pregnancy outcome of 589 cases. The most common outcome was a live birth, noted in 75.55% of pregnancies. However, this outcome varied based on the diagnosis for which topiramate was used, with highest proportion of live births seen in patients with epilepsy. [105] The risk of major malformation with topiramate has been reported to be 4.2–9%. [105,106] Among the major malformations reported cleft lip or palate anomalies, limb, hand, or other skeletal anomalies and respiratory or cardiovascular anomalies were more frequently documented. [105] Other reports also suggest association of first trimester use of topiramate and oral cleft lip/palate anomalies. [107] Other abnormalities related with topiramate use include small for gestational age [108,109,110] and microcephaly. [109]

### Gabapentin

Animal studies have demonstrated delayed bone ossification, hydronephrosis and increased rates of hydroureter. [101] No information is available regarding its possible teratogenic effects in humans. Ohman *et al.* [111] evaluated the outcome of 6 pregnancies in women receiving gabapentin during pregnancy and reported uneventful deliveries with birth to healthy children in 5 out of the 6 pregnancies. In 1 pregnancy, there was a premature delivery at 33 weeks of gestation. In terms of postdelivery complications, mild hypotonia and cyanosis was seen in 1 infant, which started 8 h after delivery. However, the infant was discharged from hospital after 4 days in a completely normal state. One recent study compared the pregnancy related outcome of 223 gabapentin exposed pregnancies with unexposed pregnancies and reported higher rate of preterm birth and low birth weight with gabapentin. Further those neonates who were exposed to gabapentin near the delivery more frequently required neonatal intensive care treatment. Two neonates exposed to gabapentin were also reported to have suffered from poor neonatal adaptation. [112]

With regard to transplacental transfer of gabapentin Ohman *et al.* [111] reported accumulation of gabapentin with umbilical cord/maternal plasma concentration ratios ranging from 1.3 to 2.1 (mean - 1.7). However, the gabapentin plasma concentrations declined with an estimated half-life of 14 h in the newborns. Studies which have estimated the concentration of gabapentin in milk suggest that mean milk/maternal plasma concentration ratio is 1.0 (range, 0.7–1.3) from 2 weeks to 3 months. Accordingly, the infant dose is estimated to be 0.2–1.3 mg/kg/day, which is about 1.3–3.8% of the dose received by the mother. When the plasma concentrations in the breast-fed infants were estimated, it was reported that the concentration in the infant was about 12% of the mother's plasma levels. However, this concentration was not associated with any adverse effects.

### Atypical antipsychotics

Atypical antipsychotics are quite frequently evaluated for the treatment of various phases of mood disorders. However, there is relatively little data available with regard to the safety of these agents in pregnancy and lactation. In this section, the data with regard to use of atypical antipsychotics in pregnancy



and lactation is reviewed, irrespective of the disorder in which these were evaluated.

### Olanzapine

Animal studies done in rodents did not reveal any evidence of teratogenicity with olanzapine despite the use of doses higher than those used clinically. There are few studies which have evaluated the use of olanzapine during pregnancy. Goldstein *et al.* [113] reported outcomes of 37 olanzapine-exposed pregnancies ascertained prospectively. Of the 37 pregnancies, 14 were terminated by therapeutic abortions with no abnormalities reported in the fetus. In the rest of the pregnancies ( $n = 23$ ), normal birth without complications occurred in 16 cases; spontaneous abortion occurred in 3; stillbirth in 1; prematurity in 1; postmaturity in 2 cases, with one of new born developing perinatal complications in the form of meconium aspiration after cesarean section; and no major malformation in any case. The rates of complications were less than or comparable to the range of base rates for general population. Additionally, the authors also reported 11 retrospectively identified cases, in which major malformations in the form of dysplastic kidney (1 case) and Down syndrome (1 case) was found. There were 2 spontaneous abortions and 1 fetal death. Perinatal complications were noted in 3 cases and postperinatal complications in 2 cases. Overall, out of 11 cases, no complications were observed in only 1 case. In a review, Gentile [114] reviewed the data of 248 reported cases on olanzapine maintained by the manufacturer (Eli Lilly) up to December 2006. Among these, spontaneous abortion was reported in 24 cases and perinatal complications in 49 cases. Various malformations which had been recorded include renal malformation ( $n = 5$ ), additional thumb digit ( $n = 2$ ) and one case each of bilateral talipes, spontaneous abortion of severe deformed fetus, pretragus fibrochondroma, clubfoot, anencephaly, absent heart, cleft palate, ventricular septum defect, albino infant, esophageal atresia, myelomeningocele plus hydrocephalus, and absent fingers. However, it was also noted that some of the cases in which malformations were found had also received other concomitant medications. Further, the authors pointed out that the manufacturer concluded that the prevalence of adverse pregnancy outcome did not differ from that found in the general population. In a recent review of data maintained by Eli Lilly, outcome of data of 610 pregnancies exposed to olanzapine was presented. The authors reported normal birth in two-third (65.7%) of cases, premature birth in 9.8%, spontaneous abortion in 9.3% and congenital anomalies in 4.4% of pregnancies and perinatal complications were seen in 8% of pregnancies. [115]

Levinson *et al.* [116] found 8 live births with no malformations, 1 spontaneous abortion, and one stillbirth. In a study which evaluated the outcome of 79 olanzapine exposed pregnancies, major malformations in the form of craniosynostosis and ureteral reflux ( $n = 1$ ), hand/finger reduction ( $n = 1$ ), ventricular septum defect and upper alimentary tract malformation ( $n = 1$ ) were observed. [117] In another study involving 60 pregnancies exposed to olanzapine, 1 case of major malformation (midline defects, cleft lip, encephalocele, and aqueductal stenosis) was reported. [118]

Various other case reports and case series have also reported birth of healthy infants without complications despite prenatal exposure to olanzapine. [119,120,121,122,123,124,125,126,127,128,129,130,131,132] A few case reports have reported defects in the form of atrioventricular canal defect and unilateral clubfoot, [133] hip dysplasia, [134] meningocele and ankyloblepharon [135] and microcephaly and anophthalmos. [136] In some of these studies, case series and case reports development or worsening of gestational diabetes mellitus was also noted. [125,126,127] Perinatal syndrome reported with use of olanzapine in pregnancy includes preterm delivery, low birth weight, hypotonia, neonatal respiratory complications, neonatal cardiovascular complications, [129] Erb's palsy, jaundice [128] and high birth weight/large for gestational age. [128,129] With respect to the postnatal long-term effects, Gati *et al.* [137] did not find any postnatal behavioral sequelae in children up to the age of 6–10 years.

Few studies have evaluated the excretion of olanzapine in breast milk. The relative dose in infant has been

reported to be in the range of 0.66–1.19%. [138,139] Data from about 40 cases are available with respect to olanzapine use during breast feeding. Goldstein *et al.* [140] reported 26 cases in which breast feeding was continued for 1–8 months. Four infants developed adverse reactions in the form of jaundice and sedation (1 case), shaking, poor sucking and lethargy (1 case), protruding tongue (1 case) and diaper rash, diarrhea, and sleep disorder (1 case). Kirchheiner *et al.* [120] reported temporary motor delay in a case whose mother took olanzapine 10 mg/day during the lactation. However, other case reports and case series have not reported any untoward effects on the infant with continuation of olanzapine in the dose range of 2.5–20 mg/day during breast feeding. [128,138,141,142] In the recently published study, data were available for 102 newborns/infants exposed to olanzapine through breast milk. Adverse outcome in the neonate or infant were reported in 15.6%, with commonly reported adverse events in the form of sedation (3.9%), irritability (2%), tremors (2%) and insomnia in 2% of neonates/infants. [115] Studies that have followed up children exposed to olanzapine through breast milk at 1–2 years of age, report no increase in adverse outcomes when compared to control group. [143]

### Risperidone

Animal studies in rats have shown increased incidence of pup deaths and stillbirth with use of risperidone during pregnancy. [101] Rosengarten and Quartermain [144] reported impaired learning and disrupted short-term retention in adulthood with use of risperidone in dam during pregnancy. In their study of 49 risperidone exposed pregnancies in humans McKenna *et al.* [118] did not report a single case of major malformations. Similarly, many studies have reported no major malformations with use of risperidone. [145,146,147,148,149,150] However, there are a few case reports of agenesis of corpus callosum, [101] and spontaneous abortions. [116] Reis and Källén [117] reported 1 case of major malformation (anal atresia along with pulmonary malformation) in 51 risperidone exposed pregnancies. The postmarketing surveillance data of 713 pregnancies (prospective data for 516 and retrospective data for 197 pregnancies) exposed to risperidone was reported. Majority of the adverse pregnancy and fetal/neonatal outcomes were reported for pregnancies for which retrospective data was available. Among the prospectively reported, out of the 68 pregnancies with known outcome, organ malformations were observed in 3.8% and spontaneous abortions occurred in 16.9% pregnancies. When compared to the general population, the rates were comparable. [151] Of the retrospectively reported outcome major organ malformations were reported in 12 pregnancies. Major malformations reported included cleft lip/palate ( $n = 2$ ), and one case each of esophageal atresia along with ear pinna hypoplasia and slight facial dysmorphism, Ivemark syndrome, Moyamoya disease, ventricular cyst in the brain, patent foramen ovale, hypoplastic left heart, dilated cardiomyopathy, right auricular achondroplasia, mild talipes equinovarus, gastroschisis, and Pierre-Robin syndrome. However, it is important to remember that in some cases in which major malformations were seen, the mothers also received other concomitant medications. [151] In terms of neonatal outcome, McKenna *et al.* [118] concluded that there was no difference in the prevalence rate of poor pregnancy outcome and perinatal complications between the risperidone exposed group and a control group exposed to nonteratogens. In the postmarketing surveillance study, [151] perinatal syndrome (in the form of tremor, jitteriness, irritability, feeding problems) was reported in 37 pregnancies, of which 21 cases involved behavioral or motor disorders. Other adverse pregnancy outcomes reported with use of risperidone include oligohydramnios, [150] small for date, [152] and gestational diabetes mellitus. [117] A case report of neuroleptic malignant syndrome in a pregnant women receiving risperidone has also been documented. [153]

With regard to use of risperidone during lactation, studies suggest that relatively low infant dose (0.84–4.7%) of the weight adjusted maternal dose [154,155] and an additional 3.46% of its metabolite are transferred to infant. [155] The data does not suggest any untoward neurodevelopmental problems with risperidone. [150,155,156]

### Quetiapine

Delay in skeletal ossifications, reduced fetal weight, and increased fetal and pup deaths have been reported with use of quetiapine in pregnancy in animal models.[101] In human studies, quetiapine has been shown to have the least placental passage (23.8%) compared to both first generation antipsychotics (haloperidol) and other second generation antipsychotics (risperidone and olanzapine). Most of the human studies have not reported any major malformation or neonatal problems with use of quetiapine in pregnancy.

[157,158,159,160,161,162,163,164,165,166,167,168] McKenna *et al.*,[118] reported on the data maintained by the manufacturer till March 2005. A total of 446 pregnancies were exposed to quetiapine. In terms of congenital malformation, out of the 151 pregnancies for which outcome was reported, 8 pregnancies had congenital malformations; with no commonality between the malformations seen. It is important to note that concurrent medications were used in 7 of the 8 cases with congenital anomalies. In a postmarketing surveillance study, out of the 6 cases, spontaneous abortion was reported in 2 cases.[157] McKenna *et al.*[118] also reported the outcome of 36 pregnancies exposed to quetiapine. Although the authors did not report any specific congenital anomalies associated with quetiapine, they concluded that compared to a control group of women exposed to nonteratogenic agents, quetiapine was not associated with an increase of teratogenic risk.

With regard to excretion of quetiapine in breast milk, studies suggest relatively low dose (0.09–0.43%) of the weight adjusted maternal dose in infant[161,169] and the quetiapine concentration in infant's plasma is estimated to be about 6% of the maternal drug concentration.[169]

### Amisulpiride

Data from animal studies on mice and rabbits show lack of teratogenic effect of amisulpiride with doses up to 4 times the maximum recommended human dose.[114] However, data on the effect of amisulpiride on human pregnancies are lacking.

### Ziprasidone

Use of ziprasidone in animals suggests its association with developmental delays, possible teratogenic effects (cardiac, renal, and skeletal), and increased still births.[101] One case report presented the association of ziprasidone with cleft palate,[170] whereas another case report reported on adverse outcome of use of ziprasidone along with citalopram during pregnancy and lactation.[171]

### Aripiprazole

In animal studies aripiprazole has shown developmental toxicity, including possible teratogenic effects in rats and rabbits. The main effects were delayed skeletal ossification and decreased fetal weight with 3–10 times the maximum recommended human dose.[172] Only 13 case reports and 1 small case series (3 cases) have discussed the outcome of aripiprazole exposed human pregnancies.

[173,174,175,176,177,178,179,180,181,182,183,184] In all cases except one, no teratogenic effects were reported. However it is important to note that in 9 out of the 16 pregnancies aripiprazole was started after first trimester of gestation. In one case minimal hip dysplasia was documented.[184] In terms of neonatal and obstetrical outcome, 1 case required caesarean section due to development of unexplained fetal tachycardia.[174]

Sparse data are available with regard to use of aripiprazole during lactation. Animal studies suggest that aripiprazole is excreted in milk. One case report suggests failure of lactation in women treated with aripiprazole in pregnancy.[173] Another case report suggested lack of aripiprazole secretion in breast milk.[178]

## Clozapine

Clozapine is the only antipsychotic which belongs to category B of FDA classification. Animal studies in rats and rabbits reveal no harm to the fetus with doses of approximately 2–4 times higher than the human dose (clozapine prescribing information).<sup>[114]</sup> Data with regard to use of clozapine in human pregnancy is available only in the form of case reports/series and occasional review. Waldman and Safferman<sup>[185]</sup> reported at least 15 normal births following maternal exposure to clozapine in pregnancy. Many others also suggest no definitive association between maternal exposure and congenital anomalies in humans.<sup>[186,187,188,189,190,191,192]</sup> A study which reported outcome of 61 pregnancies exposed to clozapine revealed 5 congenital malformations and 5 perinatal syndromes.<sup>[193]</sup> Various other associations reported with maternal exposure are decreased variability of fetal heart rate,<sup>[194,195]</sup> delayed peristalsis,<sup>[196]</sup> delayed speech acquisition,<sup>[197]</sup> floppy infant syndrome,<sup>[188]</sup> gastroesophageal reflux disease,<sup>[198]</sup> intrauterine growth retardation with oligohydramnios and intrauterine death,<sup>[199]</sup> neonatal seizures<sup>[189]</sup> and new onset or worsening of gestational diabetes mellitus with shoulder dystocia.<sup>[185,187]</sup> However, many of these findings have been complicated by the concomitant use of other drugs, malnutrition or family history of diabetes mellitus. Clozapine overdose during pregnancy has also been shown to lead to fatal poisoning in the newborn<sup>[200]</sup> and to be associated with absent fetal heart rate variability and delayed peristalsis in the newborn.<sup>[201]</sup>

As with other antipsychotics, data with regard to use of clozapine during lactation is sparse. In one case series, 2 out of the 4 infants breast-fed by mothers receiving clozapine, developed adverse events. In a case report, delayed speech acquisition was reported in the new born whose mother received clozapine during pregnancy and lactation.

## Benzodiazepines and pregnancy

Benzodiazepines are used commonly in subjects with bipolar disorders as adjunctive medications for mood stabilization, agitation, and sleep problems. All benzodiazepine compounds diffuse readily across the placenta to the fetus and are secreted in breast milk. The amount excreted depends on the oral bioavailability, plasma protein binding, maternal blood concentrations, ionization, molecular weight, half-life, degree of lipophilicity and pharmacokinetics of each benzodiazepine.<sup>[202]</sup> The use of benzodiazepines in pregnancy has been reviewed in detail by Iqbal *et al.*<sup>[202]</sup> The most important issues associated with use of benzodiazepines in pregnancy shall be discussed here.

The risk of malformation is highest if the fetal exposure occurs between 2 and 8 weeks of pregnancy. Further if benzodiazepines are given at or near term, they may cause fetal dependence and eventual withdrawal symptoms.<sup>[202]</sup>

## Diazepam

In a review of 599 oral clefts it was shown that use of anxiolytics, mostly diazepam, during the first trimester of pregnancy was associated with development of oral clefts.<sup>[203]</sup> However, this has not been a consistent finding in the later studies, with some reporting similar association,<sup>[204,205,206]</sup> while others not finding the same.<sup>[207,208,209,210]</sup> There are case reports of other malformations, however, some of these have been inconclusive because of use of other medications along with diazepam.<sup>[202]</sup> Use of high doses of diazepam (usually more than 30–40 mg/day) during labor has been associated with withdrawal symptoms starting within a few days to 3 weeks and lasting up to several months in neonates. The withdrawal symptoms are characterized by hypertonia, hyperreflexia, restlessness, irritability, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, suckling difficulties, apnea, risk of aspiration of feeds, diarrhea and vomiting, and growth retardation. Other reports suggest that use of high doses may also be associated with “floppy infant syndrome” characterized by

withdrawal symptoms, hypothermia, lethargy, respiratory problems, and feeding difficulties.[202] Use of diazepam during late pregnancy and labor has also been associated with development of prolonged hyperbilirubinemia of the newborn and potentially to kernicterus. This has been linked to the preservative (sodium benzoate) in the diazepam formulation, which competes with diazepam for plasma protein binding.[202]

Although occasional reports have associated the therapeutic use of diazepam with congenital malformation, the bulk of the evidence indicates that the use of diazepam during gestation has no adverse effects on the child's development if used in low doses.[202] However, it is to be remembered that when it is used near term, the dosage should be tapered off over weeks to avoid development of neonatal withdrawal and floppy infant syndrome.

Low dose use of diazepam either just before the delivery or during postpartum by the mother is associated with sedation in the new born. In general, low concentration of diazepam has been found in breast milk; however, the concentration varies with maternal dose. Use of higher doses of diazepam during breast feeding is associated with lethargy and weight loss in the neonate, which improves after stopping breast feeding. Hence, while using diazepam during pregnancy or labor the treating doctors should be aware of the side effects and must take appropriate measures.[202]

### **Clonazepam**

Use of clonazepam in pregnancy has been shown to be associated with apnea, bilateral inguinal hernia, congenital heart disease, cyanosis, hip dislocation, hypotonia lethargy, paralytic ileus of the small bowel, undescended testicle, uteropelvic junction obstruction, and ventral septal defect.[202] However, it is important to note that in most cases clonazepam was used along with other antiepileptics like phenytoin and barbiturates.

Use of clonazepam during lactation has also shown to be associated with apnea, CNS depression, cyanosis, excessive periodic breathing and hypotonia. Hence, clonazepam should be used during pregnancy and lactation only when the clinical benefit to the mother justifies the risks to the fetus and newborn. If used, the fetus and the newborn should be closely monitored.[202]

### **Lorazepam**

Use of lorazepam during pregnancy has been associated with anal atresia and neonatal withdrawal symptoms. The latter can be severe, because of the short half-life of lorazepam, and are characterized by low Apgar scores, depressed respiration, hypothermia, poor suckling and jaundice. Thus, injectable lorazepam should be avoided during pregnancy as far as possible.[202] Oral lorazepam should be used during pregnancy only in life-threatening situations or in cases of severe disease for which other safer drugs cannot be used or are ineffective.

In breast milk, lorazepam is secreted in low quantity and is considered to be relatively safe.[202]

### **Alprazolam**

Use of alprazolam in pregnancy has not been shown to be associated with increased risk of major malformations. However, it has been linked with malformations like ankle inversion, cat's eye with Pierre-Robin syndrome, cleft lip, congenital hip dislocation, cryptorchidism, Down's syndrome, fused lacrimal duct, hypospadias, inguinal hernia, lipomeningocele, microcephaly, patent ductus arteriosus, pyloric stenosis, strabismus, tracheoesophageal fistula, umbilical hernia and neonatal withdrawal syndrome. Thus, it should preferably not be used in first trimester and during lactation.[202]



## MANAGEMENT OF BIPOLAR DISORDERS IN PREGNANCY AND LACTATION

Clinicians handling the bipolar disorders are usually faced with the following situations:

- A patient of bipolar disorder on medications wanting to conceive
- A patient of bipolar disorder already conceived (on/not on medications), but the symptoms are under-control
- A patient of bipolar disorder already conceived (on/not on medications), but the symptoms are present/experiencing relapse
- First episode mania during the pregnancy
- First episode mania during the early postpartum period
- Continuation of medications during lactation.

There is no single answer to all the above situations. All the decisions about continuation or initiation of treatment during pregnancy in subjects with known bipolar disorders must take into account: (i) The highly variable, but often poorly quantified risks of fetal exposure to drugs (ii) the substantial risks to the patient, fetus, and family from untreated illness in the mother; and (iii) high risk of relapse associated with discontinuation of maintenance treatment, particularly if it is done abruptly. Each of these risks should be discussed in detail with the patient and her spouse and other close family members.

If a woman with bipolar disorder, who is on medication, expresses her wish to conceive, the clinician should take into consideration the illness history, acceptability and estimated safety of specific clinical interventions, which may be pharmacologic or nonpharmacologic. Specific considerations include the frequency and severity of previous episodes, past and current levels of functioning or impairment, past and recent duration of clinical stability with and without medication, the nature of prodromal symptoms that indicate an impending relapse, and average time to recovery following re-introduction of treatment. In the assessment process, it is also important to assess the usefulness of previous medication trials in terms of responses rate, adverse effects and effect of discontinuation of treatment.[15] In addition to assessing the illness and the effectiveness of current and past treatments, clinicians should also take into consideration other risk factors (e.g., poor nutrition, smoking, alcohol use etc.), which can contribute to poor perinatal outcome. Emphasis should also be on promotion of healthy behaviors like adherence to a prenatal vitamin regimen and regular prenatal checkups and healthy diet.[211]

If a woman with bipolar disorder plans to conceive, following options can be considered: Discontinue the mood stabilizer prior to conception, continue treatment until pregnancy is verified or continue treatment throughout the pregnancy. All these decisions would depend on the severity of illness and past treatment response. Discontinuation of mood stabilizer during the pregnancy phase may be considered if there is past history of one or infrequent episodes with long period of remission. If such an attempt is made it is important to remember that the pharmacological agents should be tapered off slowly and the women should be closely monitored for conception and relapse of symptoms. An alternative strategy is to continue treatment until pregnancy is verified, and then gradually taper off the mood stabilizer. Uteroplacental circulation is not established until approximately 2 weeks postconception and the early risk of fetal exposure is minimal. The advantages of this strategy are that it minimizes fetal exposure to drugs and extends the protective treatment up to the time of conception.[15] However, it is important to remember that this strategy may lead to relatively abrupt treatment discontinuation, thereby placing the patient at increased risk for relapse.[13,19,29]

In ideal situation, the patient should discuss about her plan of pregnancy and this should be when the patient is euthymic. Based on the patient's history, decision should be taken about continuation of medication during the period before conception and during the first trimester. If the patient is clinically

stable an attempt to discontinue the mood stabilizer prior to conception should be taken.

If there is recurrence of symptoms during the discontinuation trial, then a difficult choice to continue taking medication during pregnancy has to be made.<sup>[211]</sup>

If on the basis of history the illness is considered to be severe (chances of relapse are high without medication), then the psychiatrists should discuss with the patient and the spouse about continuation of mood stabilizer during the conception period also. In some cases, mood stabilizers could be continued till the confirmation of conception and then these could be withdrawn cautiously, but close monitoring for relapse should be done.<sup>[211]</sup> For women with severe forms of bipolar disorder, for example, multiple severe episodes and especially with history of psychotic symptoms and suicidal attempts, maintenance treatment with a mood stabilizer before and during pregnancy may be the safest option. In such a situation, lowest effective dose of a medication must be used and medications which have the least teratogenic potential should be selected. However, in certain cases of refractory illness, in which the patient has responded to a newer agent for which reproductive safety data are not available or is sparse, the clinician should consider to continue the same agent after explaining the pros and cons of continuing the same medication to the patient and family.<sup>[15]</sup>

If the patient is on lithium, valproate or carbamazepine before conception, the risk should be discussed with patient and spouse and wherever possible these should be stopped during the first trimester or be replaced by other safer options like a typical antipsychotic. It is important to remember that typical antipsychotics increase prolactin levels and thereby disrupt the menstrual cyclicality and hence adversely affect fertility;<sup>[211]</sup> so whenever possible, an agent with less effect on prolactin and better teratogenicity safety profile should be preferred.

For women who tolerate discontinuation of maintenance treatment, the decision when to restart the treatment depends on the clinician and the patient. Some patients and clinicians may prefer to wait for the initial signs and symptoms to appear before restarting medication, while others may prefer to limit risk of a major recurrence by restarting treatment after the first trimester of pregnancy. If the treatment has to be restarted, the decision about the mood stabilizer should take into consideration the past history of response and the risk associated with a particular agent during the second and third trimester. It is generally considered that if a woman has done well on a particular mood stabilizer then changing the mood stabilizer for avoiding potential risk to offspring may risk the woman stability and may not be a right decision. Hence, continuation of the same mood stabilizer with informed consent of the patient and spouse should be preferred. If the recurrence of symptoms during pregnancy is in the form of mild to moderate depression, psychotherapeutic interventions may be tried before considering the mood stabilizer depending on the patient's motivation for such therapy and past response. However, if the depression is severe, antidepressants (a selective serotonin reuptake inhibitor [but not paroxetine]) or electroconvulsive therapy can be considered.<sup>[15]</sup>

### **Unplanned pregnancy**

Unfortunately, about 50% of pregnancies in women with bipolar disorders are unplanned. In many instances, pregnancy is detected during or after the highest risk period for some agents has passed. Discontinuation of the medication after the risk period has passed may place the woman at risk without conferring any appreciable benefit. The variables which must be taken into account while finalizing the treatment plan include the clinical stability of the patient, duration of pregnancy, psychotropic agent which the patient is taking and treatment preferences of the patient.

If the patient has not completed the first trimester and reports with confirmed pregnancy, the pros and cons about the medication continuation and abrupt stoppage of medication have to be discussed. If the patient is

on anticonvulsants, then a high dose of folic acid should be prescribed for the woman. If it is not possible to stop the medication then attempt should be made to reduce the dose to minimum.

If the patient has completed the first trimester of pregnancy, then the patient and the spouse should be explained about the pros and cons of continuation of pregnancy, depending on the agent, which the patient was taking. If the patient had been on polypharmacy, then the additional risk should be emphasized.

If the decision to continue the pregnancy is made, the decision about the mood stabilizer should take past history of response and the risk associated with a particular agent during the second and third trimester. Continuation of the same mood stabilizer with informed consent of the patient and spouse should be preferred. However, some authors suggest that if the woman is on valproate and if there is no history of nonresponse to lithium, the switch to lithium should be considered.[212]

### **Monitoring while continuation of mood stabilizers during pregnancy**

If mood stabilizers are continued during pregnancy, prenatal screening for congenital malformation with a high resolution ultrasound and fetal echocardiography is recommended around 16–18 weeks of gestation to screen for cardiac anomalies. The possibility of fetal neural tube defects should be evaluated with maternal serum alpha fetoprotein and ultrasonography. In addition, use of folic acid is recommended prior to conception and during the first trimester for women receiving anticonvulsants, although it is unknown whether supplemental folic acid can reduce the risk of neural tube defects in the setting of anticonvulsant exposure.[49,213] For patients who are continued on carbamazepine or oxcarbazepine, Vitamin K supplementation (10 mg/day orally) during the last month of pregnancy is recommended. The new born should also receive 1 mg of Vitamin K intravenously or intramuscularly on day 1 after delivery.[76]

### **Monitoring while continuation of mood stabilizers near the term/labor**

Some experts suggest that the dose of lithium should be reduced at the onset of labor to avoid toxicity resulting from the rapid reduction of vascular volume at delivery.[214] Close monitoring of symptoms and serum lithium levels are required to avoid relapse or toxicity during delivery and the immediate postpartum period.[13,29]

### **Treatment during postpartum**

Puerperium is the period of heightened risk of relapse for subjects with bipolar disorders. Hence, restarting of mood stabilizer during immediate postpartum should be considered strongly in subjects with high risk of relapse, as data show that use of lithium as a prophylactic agent in the postpartum period reduces the rate of relapse from nearly 50% to <10%. [215,216]

### **First episode during pregnancy and puerperium**

For women who develop first episode of mania during pregnancy, the psychiatrist is called upon to decide about which medication to start. In such a scenario, the decision about the mood stabilizer is a tricky one and should take into consideration the severity of symptoms, risk to the mother and the fetus. If the patient has not completed first trimester of pregnancy, typical high potency antipsychotic or atypical antipsychotic like clozapine, olanzapine or risperidone should be tried before considering lithium, valproate or carbamazepine. If the women has completed first trimester, then also antipsychotic should be preferred over lithium (because of risk associated during labor), valproate (long-term cognitive side effects) and carbamazepine. If one of these 3 agents has to be used during the second or third trimester, lithium should be preferred over carbamazepine and valproate. The patient and the spouse should be explained about the risk with such medications. If one has to use benzodiazepines, they should be used for shortest possible duration in minimal dose and should preferably be tapered off slowly with monitoring of fetus.

### Breast feeding with mood stabilizers

Whether to allow breast feeding while continuing mood stabilizers is a difficult decision. Breast feeding is very important for development of emotional bond and attachment between the mother and the infant. [22,23] Further, it confers many physical health benefits to the mother and the newborn. Hence, risk benefit analysis should take into consideration the physiological and psychological benefits of breastfeeding, wishes of the mother, risk of infant exposure to the medication, and the possibility that a severely ill mother may forego treatment rather than give up breastfeeding.[25]

While continuing breast feeding with mood stabilizers, the infant should be clinically monitored to minimize the risk. Before starting breast feeding, the infant should be evaluated by a pediatrician for baseline behavior, sleep, feeding, and alertness. Parents should be alerted to the side effect profile of medications, and regular clinical monitoring should be done by the pediatrician to ensure normal development. It is to be remembered that metabolism and elimination are more efficient in older infants, who generally sleep for longer durations, permitting dosing of the mother just after nursing and before the baby's longest sleep interval. A close liaison must be kept with the pediatrician who can be educated about the potential side effects of medication exposure and interactions with other medications typically prescribed to infants (e.g., antibiotics, nonsteroidal antiinflammatory agents, and acetaminophen).[25]

While using a mood stabilizer, the clinician should titrate the dose to the minimum effective dose. However, in such an attempt clinician should not end up in using ineffective dose and exposing the neonate to the medication unnecessarily. If any medication is used on as and when required basis then short-acting agents should be preferred. Further, it is best to use medications in which the parent compound does not metabolize into several generations of active compounds.[25]

According to the American Academy of Pediatrics, breastfeeding should be undertaken with caution by women undergoing lithium treatment. The breast-fed infant should be monitored for serum lithium levels, electrocardiogram and complete blood counts. With regard to valproate and carbamazepine both American Academy of Neurology and American Academy of Pediatrics support breastfeeding if the mother is taking valproate,[76,77] but the liver function tests and blood counts of the newborn need to be monitored. With regard to lamotrigine, the emerging data suggest that it may be relatively safe during breast feeding. It should be used during lactation when other safer options are not available. Data for other anticonvulsants is preliminary. Data with regard to atypical antipsychotics are also preliminary and inconclusive.

### CONCLUSION

From the literature, it is evident that the safety of mood stabilizers in pregnancy is still unresolved. The decision to prescribe them during pregnancy should be taken in light of severity of mental disease and drugs should be prescribed only when the potential risk to the fetus from exposure to medication is outweighed by the risk of untreated maternal disorder. The choice of drug should depend on the balance between safety and efficacy profile. Whenever patient is on psychotropics, close and intensive monitoring should be done. An algorithm of treatment options should take into consideration the severity of illness and the individual patient's unique treatment needs.

### Footnotes

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