

The Treatment of Bipolar Disorder during Pregnancy and the Postpartum Period

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Sinan GÜLÖKSÜZ¹, Fisun AKDENİZ², Bahri İNCE¹, E. Timuçin ORAL³

Abstract

The prevalence of bipolar disorder (BD) in males and females is almost equal. The onset of BD in females typically occurs during the reproductive years, complicating its treatment. Although it was once believed that pregnancy prevents recurrence, studies have shown that recurrence is common and severe during pregnancy. On the other hand, the effects of pharmacological treatment on obstetrical outcome are not well known and some of these agents are considered teratogenic. Thus, the decision to treat pregnant patients with psychotropic agents requires solving an ethical dilemma. Risk-benefit decisions should be made while considering both the risk of relapse of BD and its morbidity, and the risk of fetal exposure to psychotropic medications. Moreover, the risk of recurrence increases dramatically in the postpartum period. It is well known that all of the psychotropic medications studied enter the breast milk. Thus, their effects on infants should be considered while prescribing for a breastfeeding mother.

The aim of this review was to discuss the safety profiles of the treatment options for pregnant and breastfeeding BD patients. Firstly, each medication's effects on organ dysgenesis, neonatal toxicity, and neurobehavioral development, and their associated adverse events during pregnancy and the postpartum period are discussed, with a focus on the emerging literature. Given this background, practical suggestions on tailoring treatment in BD patients, from preconception to breastfeeding are highlighted.

Key Words: Postpartum, Pregnancy, Bipolar Disorder, Treatment, Breastfeeding, Psychotropic Medications

INTRODUCTION

The prevalence of bipolar disorder (BD) in males and females is nearly equal. Various studies have indicated that prevalence rates vary between 0.9% and 1.7%. The lifelong prevalence rate of BD spectrum is 6% (Goodwin and Jamison 2007). BD has the highest suicide rates of all the mental disorders (Baldessarini and Tondo 2008) and causes serious dysfunction (Kessler et al. 2005). BD onset during the reproductive years causes additional difficulties in the treatment of female patients

Various studies indicate that the risk of recurrence of BD decreases with pregnancy, which is compatible with conventional opinions (Grof et al. 2000); however, some recent studies (Viguera et al. 2000, Akdeniz et al. 2003) do not support that opinion and indicate that the course

of BD is exacerbated, and that the risk of recurrence increases during pregnancy. One should consider that every manic/depressive episode during the pregnancy affects not only the patient, but can also have serious effects on the fetal health (Viguera and Cohen 1998, Altshuler et al. 2003). A treatment plan that includes follow-up is recommended for BD patients that are planning to become pregnant (Yonkers et al. 2004, Dodd and Berk 2006). Because most pregnancies occur spontaneously, treatment of these patients is associated with some difficulties.

The postpartum period is also associated with difficulties in the treatment of female BD patients. Numerous studies report that the course of BD worsens during gestation and there is consensus concerning increased

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¹MD/Resident, ³Assoc. Prof. Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Rasit Tahsin Mood Disorders Unit, Istanbul, ²Assoc. Prof., Ege University Medical Faculty Psychiatry Department: Affective Disorders Unit., Izmir.

Sinan Gülöksüz MD., e-mail: sguloksuz@yahoo.com

BD recurrence rates and severe bipolar periods during the postpartum period (Terp and Mortensen 1998, Viguera et al. 2000). The risk of recurrence increases, in particular, in women that stop their treatment during the postpartum period (Viguera et al. 2000). On the other hand, nearly half of all depressive/manic episodes during the postpartum period begin during the gestation period. Mood changes during pregnancy are one of the predictors of severe course of illness during the postpartum period (Halbreich 2004). Symptoms quickly develop a few weeks before labor or in the days following birth (Terp and Mortensen 1998); therefore, preventive treatment should begin as soon as possible following birth.

There is limited information about the teratogenic effects of the drugs used to treat BD on the fetus, and the infant during the breastfeeding period, leaving physicians with a clinical and ethical dilemma concerning their use. One should keep in mind that the gestation and postpartum periods are associated with the risk of recurrence of BD. Recurrent disease may injure the fetus and negatively affect the mother-child relationship during the postpartum period. Viguera et al. (2002) reported that physicians do not advise pregnancy to 45% of female BD patients planning to be pregnant, highlighting the ethical and clinical difficulties that physicians must contend with.

The present review aimed to present a review of recent findings and treatment plans for BD during the gestation, postpartum, and breastfeeding periods. First, the possible effects on mother and fetus of drugs used to treat the recurrence of BD are presented. Then, the effects and adverse effects of treatment options during the gestation and postpartum period will be evaluated. Critical points that should be considered when planning treatment for BD patients during gestation and the postpartum period are discussed. Anti-depressants and benzodiazepines are excluded from this review, because there are extensive number of studies on the use of anti-depressants/benzodiazepines in bipolar disorder, which should be subject of another review.

METHOD

We searched for English language publications in the Medline, PubMed, ProQuest, Cochrane, PsycINFO, and EBSCOHost databases using various combinations of the following keywords: pregnancy, pregnant, lactation, breastfeeding, postpartum, psychotropic drugs, bipolar disorder, antipsychotics, antiepileptic drugs, anticonvulsants, mood stabilizers, electroconvulsive therapy, ECT,

risperidone, clozapine, olanzapine, aripiprazole, quetiapine, ziprasidone, lamotrigine, lithium, carbamazepine, oxcarbazepine, and valproate. All publications were evaluated and those that were suitable for review were considered. References of the suitable publications were examined and relevant publications were obtained.

Evaluation of the Risks of Treatment Plans on Mother and Fetus

1. Mood Stabilizers

There is more information available about the administration of mood stabilizers during pregnancy than any other psychotropic medication. This is because lithium has been used for many years and other mood stabilizers have anti-epileptic effects. Data on valproate, carbamazepine, and lamotrigine were obtained from studies about gestational epilepsy.

TABLE 1. Classification of the risks of psychotropic medications during gestation and the postpartum period.

	Risk class during gestation ¹	Risk class during breastfeeding ²
Lithium	D	L4
Valproate	D	L2
Carbamazepine	D	L2
Lamotrigine	C	L3
Haloperidol	C	L2
Carbamazepine	C	L3
Zuclopenthixol	C	L3
Clozapine	B	L3
Olanzapine	C	L2
Quetiapine	C	L2
Risperidone	C	L3
Aripiprazole	C	L3
Ziprasidone	C	L4

¹Pharmaceutical pregnancy categories determined by the US Food and Drug Administration (FDA):

A: No risk has been observed in controlled studies; B: there is no evidence of risk; C: risk hasn't been excluded; D: there is evidence for risk; X: contraindicated in pregnancy.

²Risk classification for breastfeeding: L1: Safest; L2: safer; L3: moderately safe; L4: possibly hazardous; L5: contraindicated (Hale 2008).

1a. Lithium (Li)

Li can pass through the placenta directly to the fetus, and fetal Li levels and maternal serum levels of Li equalize. On the other hand, renal clearance of Li is low because of inadequate development of the fetal kidney and the half-life of Li is long. In other words, levels of Li in the fetus may be in the toxic range, while at the same time maternal serum levels of Li are within the treatment range (Kozma 2005).

Early studies reported that the administration of Li causes cardiovascular anomalies, such as Ebstein's anomaly, which is characterized by dislocation of the tricuspid valve to the right ventricle and various degrees of right ventricle hypoplasia at a rate 400-fold higher than in the general population (Schou et al. 1973). In particular, the development of Ebstein's anomaly increases with the administration of Li during the 2nd and 6th weeks of gestation (Gentile 2006a). Recent studies report that following the use of Li prevalence rates are 0.05%-0.1% and the risk for Ebstein's anomaly is 20-40-fold higher than in the general population: these rates are relatively low compared to earlier studies (Jacobson et al. 1992, Cohenet et al. 1994). Additionally, the development of heart and pulmonary vascular anomalies in fetuses exposed to Li was reported (Kozma 2005). In a systematic review of the relationship between Li use during pregnancy and its teratogenicity it was emphasized that Li does not increase the occurrence of major malformations and only slightly increases the risk of cardiovascular malformations (Yacobi and Ornoy 2008).

Premature birth, nephrogenic diabetes insipidus, hydroamniosis (Zegers and Andriesten 2003), cyanosis, and floppy baby syndrome, which is characterized by hypotonia (Kozma 2005), temporary neurodevelopmental defects, thyroid function disorders (Schou et al. 1973, Frassetto et al. 2002), and low birth weight are fetal and newborn complications due to the administration of Li, but their prevalence rates are unknown.

If the administration of Li is going to be continued there are some points that need to be considered. Because of high glomerular filtration rates during the first trimester Li excretion increases, and to achieve therapeutic levels of Li it must be frequently administered at high doses. Attention has to be paid to conditions that increase blood levels of Li (sodium restriction, diuretic administration). In order to avoid the toxic effects of high blood levels of Li due to a sudden fall in vascular volume, the dose of Li must be reduced by 50%-75% (Yonkers et al. 2004). Li levels in the umbilical cord are the same as maternal serum levels (Newport et al. 2005); therefore, blood levels of Li must be monitored closely, both during gestation and after birth. In cases of prolonged labor the administration of intravenous fluid can be considered in order to achieve adequate hydration. Considering the harmful effects of Li to the fetus during the first trimester, the fetus must to be examined with high-resolution ultrasonography and echocardiography between the 16th and 20th weeks (Jacobson et al. 1992, Cohen et al. 1994, Altshuler et al. 1996, Yonkers et al. 2004).

The American Academy of Pediatrics in the past emphasized that the administration of Li during the breastfeeding period is contraindicated, but in recent years they have recommended careful administration of Li during breastfeeding (American Academy of Pediatrics Committee on Drugs 2001). The rate of Li levels in breast milk is around 24% to 72%, as compared to Li levels in maternal serum (Chaudron and Jefferson 2000, Burt et al. 2001). The "rule of halves" is valid in serum levels; breast milk contains about half the concentration of maternal serum, and infant serum has about half the level of breast milk (Viguera et al. 2007). Nevertheless, one must consider that Li levels can be increased with dehydration during febrile illness in newborns. In addition, the effects of Li on newborns are unknown; therefore, monitoring levels of Li in breast milk and/or newborns is suggested (Yonkers et al. 2004), though nowadays monitoring blood levels is not recommended (ACOG Practice Bulletin 2008). Babies exposed to Li via breast milk must be monitored for the adverse effects of Li (thyroid functions and renal clearance)—once per week during the first 6 weeks, and then once every 2-3 weeks (Viguera et al. 2007).

1b. Valproate (VPA)

There is consensus that the administration of VPA during gestation has teratogenic and toxic effects on the fetus (ACOG Practice Bulletin 2008). Neural tube defect is the most common teratogenic effect of VPA when administered during the first trimester (Wyszynski et al. 2005). Studies in patients with epilepsy have shown that the prevalence of neural tube defect after using VPA in the first trimester varies between 3.8% and 9%. Other fetal malformations due to VPA exposure during gestation are septo-optic dysplasia (McMahon and Braddock 1998) and congenital heart defects (Thisted and Ebbesen 1993, Sodhi et al. 2001). Fetal VPA syndrome has also been reported, which is characterized by epicanthic folds, a flat nasal ridge, anteverted nostrils, facial anomalies accompanied by a thin upper lip and thick lower lip, joint deformities, and neurodevelopmental defects (Williams and Hersh 1997, Moore et al. 2000,). Numerous studies reported the rate of major malformations after using VPA alone was between 5.8% and 20.3% (Samren et al. 1997, Kaneko et al. 1999, Samren et al. 1999, Wide et al. 2004, Artama et al. 2005, Vajda and Eadie 2005, Wyszynski et al. 2005, Meador et al. 2006, Morrow et al. 2006, Vajda et al. 2007a). In a study conducted in Turkey major malformations were observed in 2 of 15 (13.33%) babies exposed to VPA during gestation

(Eroglu et al. 2008). All of these studies show that the rate of major malformation is higher than in the general population. The risk of major malformation due to VPA is dose related (Omtzigt 1992, Samren et al. 1997, Samren et al. 1999, Mawer et al. 2002, Artama et al. 2005, Meador et al. 2006, Morrow et al. 2006, Vajda et al. 2007a); however, a study that compared different doses of VPA during gestation, in terms of the occurrence of major malformations, did not report any differences (Wyszynski et al. 2005).

Afibrinogenemia, hypoglycemia, fetal hepatotoxicity, and intrauterine hemorrhage are toxic symptoms of VPA (Majer and Green 1987, Thisted and Ebbesen 1993, Kennedy and Koren 1998). Verbal IQ in children who exposed to VPA during gestation is lower than that in children exposed to other anti-epileptics and the general population (Adab et al. 2004, Meador et al. 2007). Babies exposed to VPA require special education (Meador et al. 2007).

The use of other mood stabilizers instead of VPA is recommended in patients that have used VPA as a mood stabilizer prior to gestation (ACOG Practice Bulletin 2008); however, it is possible for a fetus to be exposed to VPA during the first trimester in unplanned pregnancies. Although it is known that folic acid support during gestation decreases the prevalence of neural tube defects, its level of prevention is unknown (Nambisan et al. 2003, Vajda et al. 2003). In pregnant women using epileptic drugs or in those with a high risk of developing neural tube defect, the administration of 4-10 mg d⁻¹ of folic acid can be started from 3 months before pregnancy and during pregnancy (Yonkers et al. 2004).

Mothers taking VPA during the postpartum period have 10%-40% of maternal serum levels of VPA in their breast milk (Von Unruh et al. 1984, Kuller et al. 1996, Chaudron and Jefferson 2000). The level of VPA in the breast milk of mothers that used VPA during gestation gradually decreased (Von Unruh et al. 1984). Thrombocytopenic purpura and anemia are observed in babies exposed to VPA via breast milk (Stahl et al. 1997). Epileptic mothers that use anti-epileptics should be encouraged to breastfeed (Holmes et al. 2001, ACOG Practice Bulletin 2008).

1c. Carbamazepine (CBZ)/Oxcarbazepine (OCBZ)

CBZ is also considered to be teratogenic, as is VPA (ACOG Practice Bulletin 2008). Studies conducted with epilepsy patients indicate that the prevalence rate of neural tube defects in babies exposed to CBZ dur-

ing gestation varies from 0.5% to 1% (Jones et al. 1989, Rosa 1991). Additionally, the prevalence rates of major malformations vary between 2.2% and 7.9% (Samren et al. 1997, Kaneko et al. 1999, Samren et al. 1999, Holmes et al. 2001, Matalon et al. 2002, Wide et al. 2004, Artama et al. 2005, Morrow et al. 2006, Vajda et al. 2007b). A study conducted in England reported that there is no increased risk of major malformation development (Morrow et al. 2006). On the other hand, a recent meta-analysis reported that using CBZ alone during gestation increased the risk of malformations 4.6-fold, as compared to the general population (Meador et al. 2008). One prospective study conducted in Turkey showed that 3 of 46 babies (6.52%) whose mothers used CBZ had MM (Eroglu et al. 2008). Contradictory results concerning the prevalence of major malformation development are related to differences in study samples and methods.

Neural tube defects, craniofacial bone anomalies, urinary system defects, cardiovascular system defects, neurodevelopmental retardation, and harelip/cleft palate are among the malformations observed in babies exposed to CBZ (Jones et al. 1989, Ornoy and Cohen 1996, Matalon et al. 2002, Dodd and Berk 2006). CBZ administration increases the risk of coagulopathy (Kaneko et al. 1999). Transient cholestatic hepatitis, direct hyperbilirubinemia, and low birth weight can be considered among the other symptoms related to CBZ administration during gestation (Frey et al. 1990, Merlob et al. 1992, Diav-Citrin et al. 2001). Numerous studies reported that neurodevelopmental defects do not occur in children exposed to CBZ during gestation. Additionally, no differences were observed between their intelligence levels and those in the general normal (Wide et al. 2002, Adab et al. 2004, Gaily et al. 2004).

Excretion of CBZ partially increases during gestation, but normal blood levels of CBZ are not much different than gestational levels (Yerby et al. 1992, Tomson et al. 1994). CBZ is not recommended for use during gestation (ACOG Practice Bulletin 2008). If it is going to be administered, controlling blood levels of CBZ during gestation is recommended. Administration of CBZ is thought to lead to vitamin K deficiency, coagulation disorders, and the development of mid-line facial defects. It is recommended to administer 20 mg d⁻¹ of vitamin K during the last month of gestation when CBZ is used (Yonkers et al. 2004). Due to the parenteral administration of 1 mg vitamin of K to all newborns, it is not possible to determine the prevalence of hemorrhagic disorder in newborns (Chouluka et al. 2004).

OCBZ is a molecule similar to CBZ. It has been suggested that the administration of OCBZ during gestation is safer than using CBZ because OCBZ lacks the epoxide metabolite and does not induce its own metabolism; however, data on the administration of OCBZ during gestation are limited. In a study that evaluated 55 pregnant women that used OCBZ, no major malformations were observed in the newborns of 35 of the women that used OCBZ alone (Meischenguiser et al. 2004). Another study showed that 2 of 37 babies had a ventricular septal defect (Sabers et al. 2004). When 248 pregnant women exposed to OCBZ were evaluated, the babies of only 6 of the women had a major malformation (2.4%); this rate of malformation does not differ from that in the general population (Montouris 2005).

If glucuronidation is altered with hormonal changes, we suggest that OCBZ metabolism should be accelerated. Blood levels of monohydroxy, a derivative of OCBZ, decreases by up to 64%-72% during gestation (Christensen et al. 2006)

CBZ levels in breast milk vary between 7% and 95% of maternal blood levels. Fetal blood levels of CBZ vary between 6% and 65% of maternal blood levels (Chaudron and Jefferson 2000). Transient cholestatic hepatitis (Frey et al. 2002) and hyperbilirubinemia (Merlob et al. 1992) developed in the babies of mothers that use CBZ while breastfeeding. Monitoring blood counts and liver enzymes is recommended in the babies of mothers that use CBZ while breastfeeding (ACOG Practice Bulletin 2008). Breastfeeding while using CBZ is considered safe (ACOG Practice Bulletin 2008). Breast milk/maternal serum level of OCBZ ratio was reported to be 0.50. During breastfeeding no adverse events occurred in the children of mothers that used OCBZ (Gentile 2003).

1d. Lamotrigine (LMT)

A study conducted with bipolar pregnant woman suggested that LMT might have a protective effect against depression during gestation (Newport et al. 2008a). Although studies conducted with epilepsy patients to determine the effects of LMT during gestation report contradictory result, LMT is considered to be relatively safe compared to other treatment options during gestation (ACOG Practice Bulletin 2008).

The prevalence rates of major malformations were reported to be between 1.0% and 3.2% by 5 studies on epilepsy patients that were using LMT during gestation (Meador et al. 2006, Morrow et al. 2006, Cunningham et al. 2007, Vajda et al. 2007b, Holmes et al. 2008). As

the prevalence rate of major malformation in the general population varies between 3% and 4%, it can be considered that LMT does not have any teratogenic effects (New York State Department of Health 2005). In a recent meta-analysis, the risk of major malformation due to LMT administration during gestation was reported as 2.91% (Meador et al. 2008). Increased risk of the development of cleft palate/harelip due to LMT was observed in another study (Holmes et al. 2008), but other studies did not observe a relationship between major malformations and LMT administration. A study that examined the relationship between LMT administration and cleft palate/harelip reported that there wasn't a relationship between the 2 variables (Dolk et al. 2008). On the other hand, LMT is associated with neonatal adaptation and thrombocytopenia (Morrow 2003). Although there are studies that suggest that the risk of major malformation increases as the dose of LMT increases (Morrow et al. 2006), other studies do not confirm this relationship (Cunnington et al. 2007).

It has been reported that metabolism of LMT in the liver increased from 65% to 230 % and blood levels of LMT decreased during gestation (Tran et al. 2002, Pennell et al. 2004, Pennell et al. 2008). Serum levels of LMT should be monitored. Symptoms of toxicity after birth indicate metabolism of LMT in the liver rapidly returns to normal (Tran et al. 2002, De Haan et al. 2004); therefore, it is recommended to return to pre-gestational dose levels during the first postpartum week (Pennell et al. 2008).

The breast milk/maternal serum LMT ratio varies between 0.35 and 0.65 (Ohman et al. 1998, Ohman et al. 2000, Liporace et al. 2004, Gentile 2005, Newport et al. 2008b). Although levels of LMT in the children of mothers that use LMT during breastfeeding reach treatment levels, no adverse events have occurred (Liporace et al. 2004, Newport et al. 2008b). Thrombosis was observed in 7 of 8 children in a study that evaluated the children of mothers that continued using LMT during breastfeeding; however, during the follow-up of these children no adverse events occurred (Newport et al. 2008b).

2. Antipsychotics

2a. First-Generation Antipsychotics (FGA)

The literature contains many studies about FGAs and as the purpose of administering FGAs during gestation is to prevent hyperemesis gravidarum, FGA doses used

in those studies were low. Additionally, in those studies anti-psychotics were used for the prevention of miscarriage. The effects of chlorpromazine during gestation are well known. There is no increased risk of major malformation with CPZ treatment in studies that used phenothiazines in order to prevent hyperemesis gravidarum (Miklovich and Van den Berg 1976, Slone et al. 1977). A systematic review showed that CPZ does not increase the risk of major malformation development (Gentile 2008a). On the other hand, exposure to phenothiazines between the 4th and 10th weeks of gestation causes major malformations (Edlund and Craig 1984; Altshuler et al. 1996). In a rare study conducted with psychotic pregnant patients no difference was observed between the 52 patients that used CPZ and the 110 patients that did not take any medication, in terms of the risk of major malformations; however there was a 2-fold higher risk of major malformation, as compared to the general population (Gentile 2008a). This result indicates that major malformations are not just due to the medication, but are also related to such variables as existing disorders, excess smoking, and lack of gestational care (Sacker et al. 1996, Bennedsen et al. 1999, Howard et al. 2003).

In a study that used haloperidol (HAL) (mean dose: 1.2 mg) in order to treat hyperemesis gravidarum the researchers observed that there wasn't an increase in the risk of major malformations and that major malformations did not affect birth weight or gestation time (Van Waes and Van de Velde 1969). There are case studies that report extremity malformations due to HAL administration. In a recent prospective cohort study that evaluated butyrophenones the risk of major malformations was normal after 2.25-10 mg d⁻¹ oral administration or 100 mg m⁻¹ intramuscularly injected HAL (Diav-Citrin et al. 2005). In the same study the development of conditions like premature labor and low birth weight were observed with butyrophenone administration. Another study showed that major malformations developed in 2 of 78 babies (2.6%) exposed to HAL 8 of 75 babies (10.7%) exposed to zuclopenthixol, and 5 of 101 (5%) babies exposed to flupenthixol during gestation (Reis and Kallen 2008).

Neonatal jaundice, intestinal obstruction after birth, arrhythmia, nutritional and respiratory problems, extra pyramidal symptoms like neuroleptic syndrome, and dyskinesia developed when FGA was administered during gestation (Collins and Comer 2003, Diav-Citrin et al. 2005) While evaluating these conditions related to FGAs we must consider that in some cases antipsychotics were administered together with anticholinergics and

antihistamines, which also play a similar role in the development of these conditions.

In a study that examined neurodevelopment in children exposed to FGAs during gestation no differences were observed at age 4 years, as compared to the general population, in terms of IQ scores (Slone et al. 1977). In another study that examined children ≤ 5 years of age no differences were observed between them and the control group (Edlund and Craig 1984). Some experts suggest that these drugs are safer than mood stabilizers and second-generation anti-psychotics (SGAs) because of the well-known risks during gestation (Altshuler et al. 1996). Some physicians recommend that pregnant BD patients in remission should use FGAs instead of mood stabilizers during the first trimester, or throughout the pregnancy (Yonkers et al. 2004)

A study conducted with breastfeeding mothers that were using FGAs showed that the breast milk/serum ratio of HAL was 2.8 in first milk and 3.6 in last milk. In same study the breast milk/serum ratio of CPZ was 1.2 in first milk and 1.6 in last milk. No toxicity has been observed in babies, but between the 12th and 18th weeks of gestation neurodevelopmental delay was observed in 3 babies whose mothers used HAL and CPZ together. On the other hand, sleepiness and lethargy has been observed in children whose mothers used CPZ while breastfeeding (Wiles 1978); therefore, some experts suggest avoiding the use of CPZ during breastfeeding (Winans 2001).

2.b. Second-Generation Antipsychotics (SGA)

Currently, data on SGAs are limited, but are increasing due to increased rates of the administration of SGAs during gestation and the postpartum period. In a prospective cohort study conducted with 151 pregnant women that were using clozapine (CLZ), olanzapine (OLZ), quetiapine (QTP), and risperidone (RIS), there were 22 spontaneous miscarriages (14.5%), 15 therapeutic curettages (9.9%), 4 stillbirths (2.6%), and 1 major malformation (0.9%) (McKenna et al. 2005). Lower birth weights were observed in the babies of mothers that used antipsychotics during gestation, as compared to the general population (McKenna et al. 2005). On the other hand, children exposed to SGAs have higher birth weights than the general population and children exposed to FGAs (Newham et al. 2008). A retrospective analysis of 16 babies exposed to SGAs during gestation reported no differences in birth weights (Wichman 2009). Major malformations, metabolic problems related to gestation, and adverse perinatal events after

CLZ administration were reported in case studies and case series limited to a small number of cases (Gentile 2008a, Reis and Kallen 2008).

Along with these findings, other studies suggest that there were no adverse events or major malformations with CLZ administration (Barnas et al. 1994, Duran et al. 2008). Major malformations were observed in 3 of 80 (3,8%) newborns exposed to OLZ (Reis and Kallen 2008). In another study 1 major malformation was reported in 60 babies exposed to OLZ (McKenna et al. 2005). A systematic review of the Lilly company database reported that there were no major malformations in their first report, but after extending the database they reported some major malformation cases, with a comparable incidence rate to that of the general population (Gentile 2008a). Case studies have reported major malformations, metabolic complications (e.g., diabetes mellitus), and adverse events after birth following OLZ administration during gestation (McKenna et al. 2005, Vemuri and Rasgon 2007, Yeshayahu 2007, Reis and Kallen 2008). Some studies reported no major malformations or adverse events after OLZ administration (Mendhekar 2002, Sharma et al. 2006).

A recent study conducted on placental transmission of antipsychotics (umbilical cord/maternal serum concentration) reported that placental transmission rate of OLZ is 72.1% (Newport et al. 2007). In the same study low birth weight was observed in 4 of 14 babies of women that used OLZ during gestation. Moreover, OLZ has the highest placental transfer rate and QTP has the lowest placental transfer rate (23.8%). A systematic review conducted with data gathered from the Astra Zeneca company database reported different types of non-uniform major malformations in 8 of 151 babies exposed to QTP during gestation (Gentile 2008a). On the other hand, some case studies and case series suggest that there are no adverse events or major malformations after QTP administration during gestation (McKenna et al. 2005, Gentile 2006b, Newport et al. 2007, Cabuk et al. 2007, Twaites et al. 2007, Reis and Kallen 2008). The rate of placental transfer of RIS is 49.2% (Newport et al. 2007). While 2 (3.9%) major malformations were observed in a study conducted with 51 women that used RIS during pregnancy, no major malformations were observed in another study conducted with 49 pregnant women who used RIS during pregnancy (McKenna et al. 2005). There are no data available on amisulpride and sertindole administration during gestation. Unexpected events and major malformations did not occur with ziprasidone administration during gestation (Wichman 2009). Tempo-

rary symptoms related to poor neonatal adaptation have been observed in 1 of 3 children exposed to aripiprazole during gestation (Mendhekar et al. 2006, Mervak et al. 2008).

The treatment of manic and mixed episodes in the postpartum period often requires antipsychotic administration. Although CLZ is the first-choice SGA, data on its administration during breastfeeding are limited. The breast milk/serum ratio of CLZ varies between 4.3 and 2.8 (Barnas et al. 1994). One study conducted with 4 breastfeeding mothers observed excessive sedation in 1 baby and agranulocytosis that remitted with cessation of drug in another baby (Trixler and Tenyi 1997). The administration of CLZ during the breastfeeding period is not recommended because of the risk of life-threatening conditions, such as agranulocytosis and an unacceptable breast milk/serum ratio (Winans 2001, Gentile 2008b). The breast milk/serum ratio of OLZ is 0.1-0.84 and serum levels of OLZ in babies are too low to be measured (Croke et al. 2002, Gardiner et al. 2003). A systematic review of the Lilly company database shows that OLZ administration during the breastfeeding period caused adverse events, such as extrapyramidal symptoms. As such, OLZ administration during the breastfeeding period is not recommended (Gentile 2008b); however, case series suggest that there are no adverse events observed with OLZ administration during the breastfeeding period (Croke et al. 2002, Gardiner et al. 2003). The breast milk/serum ratio of QTP was reported to be 0.29 (Rampono et al. 2007). Some case studies suggest there are no adverse events observed with QTP administration during breastfeeding (Gentile 2006b, Misri et al. 2006). Mild neurodevelopmental delay was observed in 2 babies in a study conducted with 6 babies exposed to QTP during the breastfeeding period (Misri et al. 2006). The breast milk/serum ratio of RIS varies between 0.21 and 0.42, and the breast milk/serum ratio of 9-hydroxyrisperidone, a metabolite of RIS, varies between 0.24 and 0.39. Furthermore, some case series suggest there are no adverse events with RIS administration during breastfeeding (Ratnayake and Libretto 2002, Ilett et al. 2004, Aichhorn et al. 2005). Data on aripiprazole, ziprasidone, and sertindole administration during the breastfeeding period do not exist.

3. Electroconvulsive Therapy (ECT)

There is consensus that ECT during gestation for the treatment of severe manic/depressive episodes is associated with fewer teratogenic effects than multiple drug administration; however, some case studies and case se-

ries reported adverse events in 25 of 339 babies whose mothers had ECT during gestation; 11 of these events resulted in death (Anderson and Reti 2009). Only 1 of these deaths was directly associated with ECT and another death had a possible association with ECT. Although complications occurred during gestation in 20 of 339 pregnant women that underwent ECT, only 4 of these complications were directly associated with ECT. While evaluating this review we must keep in mind that it contains case series that were published between 1941 and 2007, and that the use of ECT has changed since 1941. Unfortunately, there are no prospective studies on the use of ECT during gestation. In some case series ECT-related complications, such as preterm birth (Polster et al. 1999, Kasar et al. 2007) and fetal heart arrhythmia (DeBattista et al. 2003, Bozkurt et al. 2007) have been observed. In contrast, Maletzky's case series of 4 pregnant depressive women treated with ECT reported no adverse complications related to ECT (Maletzky 2004). Anesthetics and myorelaxants, which are used during ECT, are another concern because of their adverse effects on both mother and fetus. It is known that succinylcholine, which is used as a myorelaxant, has a very low placental transfer rate and does not have any teratogenic effects (Anderson and Reti 2009). Anesthetics like propofol, etomidate, and methohexital can pass through the placenta and their fetal serum levels vary (Anderson and Reti 2009). These 3 anesthetics are not associated with teratogenicity. Another point that should be considered during ECT is changing rates of estrogen/progesterone levels, which may alter the epileptic seizure threshold. Atropine administration during ECT is not recommended during gestation because it may increase the risk of gastric regurgitation, which is already high during gestation due a decrease in esophageal sphincter tonus, which may increase the risk of aspiration pneumonia. Additionally, atropine may cause fetal bradycardia (Yonkers et al. 2004, Anderson and Reti 2009). In order to decrease the risk of aspiration pneumonia, intravenous administration of antacids—like sodium citrate—that do not disintegrate into particles are recommended (Walker and Swartz 1994, Yonkers et al. 2004). Another issue that needs to be considered during ECT is the possibility of decreased blood flow to the fetus due to increased pressure of the uterus on the main arteries, which can cause fetal heart arrhythmia. This risk can be decreased by elevating the right hemipelvis of the mother; with this maneuver the uterus rotates to the left, decreasing the pressure it exerts on the main arteries.

RECOMMENDATIONS

In the treatment of female BD patients during their reproductive years, pregnancy should be carefully planned. Active contraceptive methods should be recommended to female patients that take medication. Most psychotropic medications have teratogenic effects (Table 1) and sudden cessation of medication can trigger an exacerbation the disorder's episodes; however, it is safe to taper medications gradually. The course of illness should be considered in planning a pregnancy and if it is possible, medications should be decreased to a single drug. A minimum of 1 year of symptom free period should be targeted. VPA should not be used during gestation. Besides, the medication that has been beneficial for the management of manic/depressive symptoms before pregnancy will most probably beneficial during pregnancy. The administration of medications is not recommended in the absence of sufficient knowledge of the drug's effects and patients should be monitored once per month during gestation. Relatives of the patient should be informed about the course and prognosis of the illness during pregnancy. Early symptoms should be evaluated immediately.

Reproductive functions (menstruation, examination of reproductive hormones, and ovulation follow-up) should be evaluated. Reproductive functions (for example, spermogram) of the patient's partner should also be evaluated. Patients and their partners should be informed about the course of illness during gestation and the postpartum period, the teratogenic effects of medications, and the risks of non-medication during gestation. While planning pregnancy, physicians must taper medications gradually (2 months minimum). Physicians should consider not administering any psychotropic medications, at least during the organogenesis period (first trimester) if follow-up of the patient is possible (if manic/depressive symptoms do not exacerbate). In most cases it is not possible to follow-up the patient during non-medication periods or to stop medication during an acute manic/depressive episode. The postpartum period is associated with the risk of the onset or recurrence of BD. Other biological variables, such as insomnia, may trigger attacks. Mood stabilizing drugs administered before gestation should be started again after birth.

While planning for breastfeeding, we should remember that every psychotropic medication passes into breast milk during the lactation period. Not detecting a medication in breast milk does not mean that it does not contain that medication. The levels of medication in breast milk vary, depending on its absorption, half-life, serum

peak time, levels in maternal serum, rate of binding to proteins, molecular size, pH of plasma and milk, solubility rates in water and fat, fetal development, life time, and nutrients supplementary to breast milk. Nonetheless, for most patients it is possible to take medications while breastfeeding.

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In conclusion, we should provide information on the pregnancy prevention methods for BD women during their reproductive years, and we should inform them about the course of illness and treatment during gestation. We should also teach such patients how to prevent recurrences in the postpartum period

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