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WOMEN'S MENTAL HEALTH (CN EPPERSON, SECTION EDITOR)

Bipolar Disorder in Pregnancy and Postpartum: Principles of Management

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Abstract Pregnancy and postpartum represent times of increased vulnerability for women with bipolar disorder, yet this condition remains under-diagnosed and under-treated. As 50 % of pregnancies are unplanned, the risks associated with the illness and the potential risks associated with treatment should be considered when a woman of reproductive age first presents for evaluation. This article reviews the epidemiology of perinatal bipolar disorder, screening recommendations, and treatment with pharmacotherapy and electroconvulsive therapy (ECT). An overview of the data in pregnancy and lactation is presented for lithium, lamotrigine, valproic acid, newer antipsychotics, and ECT. General principles of management include close monitoring in pregnancy and postpartum, careful adjustment of the treatment regimen to attenuate the risk of relapse, and avoidance of valproic acid when possible. Thoughtful consideration of these issues will minimize the risks to the mother and baby.

Keywords Bipolar disorder · Depression · Pregnancy · Perinatal · Postpartum · Lactation · Mood stabilizers · Antipsychotics · Teratogenicity · Neonatal complications · Neurodevelopmental effects

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Introduction

Women with bipolar disorder are at high risk for relapse during and after pregnancy [1–3]. Rapid symptom onset is common, and in the postpartum period especially, the illness may be accompanied by psychotic features [4]. Postpartum psychosis may be the first presentation of bipolar disorder [1].

Perinatal bipolar disorder is under-diagnosed, especially when the patient presents with depression [5]. Perinatal episodes may be complicated by poor prenatal care, insomnia, substance abuse, poor bonding with the baby during and after pregnancy, inability to care for the infant, obsessions regarding the baby, delusions, hallucinations, suicide, and infanticide [1]. Although the suicide rate in pregnancy is lower than in non-pregnant women, suicide is a leading cause of maternal death in pregnancy and the first postpartum year [6].

Medication management during pregnancy and lactation is complicated by concerns about teratogenicity (congenital malformations), neonatal complications, neurobehavioral teratogenicity (neurodevelopmental effects), and by changes in drug metabolism across pregnancy and postpartum. Electroconvulsive therapy (ECT) is another therapeutic option for severely ill patients but does not replace pharmacotherapy. The epidemiology of perinatal bipolar disorder, screening recommendations, and treatment with pharmacotherapy and ECT will be reviewed.

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Epidemiology

In a retrospective study evaluating the risk of recurrence in women who discontinued lithium during pregnancy compared to a group of non-pregnant women who also discontinued lithium, the rate of relapse during pregnancy was similar in both groups (52 vs 58 %) [7]. Postpartum, however, the risk of recurrence was three times greater: 70 % as compared to 24 % in the non-pregnant women who were off lithium for the same amount of time. The majority of episodes were depressive or dysphoric-mixed episodes. In the first prospective cohort study examining the risk of recurrence in pregnant women with bipolar disorder who were euthymic at conception, the rate of relapse was 85.5 % among those who discontinued their mood stabilizer [3]. The majority of episodes occurred in the first trimester, with major depression and mixed episodes accounting for 74.1 % of all episodes. Thirty-seven percent of women who remained on their medication also relapsed during pregnancy, highlighting the need for close monitoring to attenuate the risk. In addition to the discontinuation of medication, risk factors for relapse include severity of illness and previous postpartum episodes [3, 7].

Bipolar disorder is a major risk factor for postpartum psychosis. Others include a family history of postpartum psychosis, primiparity, and sleep deprivation [1]. The estimated incidence of postpartum psychosis is 1 to 2/1000 births. Autoimmune encephalitis was recently identified in a small group of women with postpartum psychosis [8]. Although rare, it may be considered part of the differential diagnosis in a patient with no prior history of psychiatric disorders or risk factors for psychosis.

Screening for Perinatal Bipolar Disorder

Screening for perinatal depression with instruments including the Edinburgh Postnatal Depression Scale (EPDS) may lead to an incorrect diagnosis of unipolar depression if screening for bipolar disorder is not also conducted [9]. The most common presentation of women with bipolar disorder during the perinatal period is a depressive episode [10]. The Mood Disorder Questionnaire (MDQ) has been the most widely studied screening tool for bipolar disorder [10, 11]. It has been validated for use in the postpartum period, but has not yet been validated during pregnancy [11]. 21.4 % of the patients who screened positive for depressive symptoms on the EPDS also screened positive for bipolar disorder on the MDQ [9].

Universal screening for bipolar disorder in pregnancy has been recommended by the Canadian Network for Mood and Anxiety Treatments (CANMAT) but is not yet recommended by the American College of Obstetricians and Gynecologists [12]. We recommend screening for women who screen positive for depression, who have a history of depression, hypomania, psychosis, anxiety disorders, or substance abuse, or who have a family history of bipolar disorder. If antidepressants are being considered, it is essential to screen for bipolar disorder. As mood instability during pregnancy is the biggest predictor of postpartum episodes, it is prudent to screen patients when they first present for care [5]. If there is a concern that the patient is suicidal, homicidal, or psychotic, the patient should be referred for immediate evaluation.

Treatment

Pharmacotherapy

The decision to use pharmacotherapy in pregnant or lactating women is predicated on the risks of untreated illness. One consideration is whether the treatment increases the risks of teratogenicity, perinatal complications, or neurodevelopmental abnormalities. According to the March of Dimes, the background rate of birth defects seen in the USA is 3–5 % [13]. As an example of the risks of untreated illness, a study from the Swedish Medical Birth Register using prescription databases reported that pregnant women with bipolar disorder, whether or not they took mood stabilizers, were more likely to be overweight or obese, to smoke, and to use alcohol and illicit drugs compared to women without bipolar disorder [14]. Rates of induction of labor, instrumental delivery, cesarean section, and late preterm birth were also higher in the groups with bipolar disorder.

Double-blind placebo controlled prospective studies with long-term follow-up to assess the safety of a given medication in pregnancy and lactation are not available. While case series are useful for generating hypotheses, they are not representative of the entire population of exposed individuals and lack a denominator for the estimation of possible risk. The prospective and retrospective studies available each have disadvantages depending on study design: participation bias, diagnostic bias, recall bias, detection bias, or incomplete ascertainment of outcomes. Few studies include validation of fetal exposure, although misclassification of exposure tends to bias the results towards the null. Most studies do not adequately control for confounding by indication, namely the effect of illness itself and comorbid conditions (such as alcohol and drug abuse) on the outcomes of interest, independent of medication exposure [14]. Studies may not control for other medication exposures or maternal factors including body mass index or mode of delivery. Studies that combine different medications are less informative than those on individual drugs.

General Principles of Management

At each visit, we recommend documenting the patient's last menstrual period and method of contraception. Make

treatment choices with the anticipation that the patient will become pregnant. Hold an informed consent discussion as soon as it is clinically feasible. Involve the partner if clinically appropriate. Carefully document the history and treatment recommendations. Monitor the patient closely, adjusting medication doses across pregnancy and postpartum to maintain a therapeutic level and avoid toxicity. Advise the patient to avoid sleep deprivation. Address psychosocial stressors. If the patient is stable and chooses to breastfeed, we recommend that someone else feed the baby at night to minimize the risk of relapse associated with postpartum insomnia.

Lithium, valproic acid, and lamotrigine have been used extensively for the treatment of bipolar disorder. Newer antipsychotics such as olanzapine and quetiapine are also used as mood stabilizers. We will present an overview of the data on these medications in pregnancy and lactation. Carbamazepine and older antipsychotics will not be discussed, nor will benzodiazepines though they are frequently necessary as adjuncts to the primary mood stabilizers.

Lithium

Congenital Malformations

The efficacy of lithium in pregnancy and postpartum has been well established [15]. Lithium freely crosses the placenta and equilibrates between maternal and cord serum [16]. An association between lithium exposure and Ebstein's anomaly was first reported in 1974 [17]. An analysis of the published data in 1994 estimated the risk to be 1 to 2/1000 live births compared to the background rate of 1/20,000 live births [18]. No causal relationship has been established. A recent prospective observational study from the Israeli Teratology Information Service reported on the outcome of 183 pregnancies with first trimester lithium exposure, 72 disease-matched controls who were untreated or taking other psychotropics, and an additional control group of 748 pregnancies with exposures considered to be non-teratogenic [19••]. First trimester lithium exposure was not associated with an increased risk of cardiovascular anomalies compared with the non-teratogenic exposure control group when anomalies that spontaneously resolved were excluded. High-resolution ultrasound and fetal echocardiography are recommended at 16–18 weeks based on the possibility that lithium therapy increases risk of heart defects [18].

Perinatal Complications

Lithium-associated perinatal complications have been reported, usually consisting of sedation. There are also reports of a "floppy infant syndrome" characterized by poor tone and cyanosis [15]. These effects may be dose related; one small prospective study reported an increased risk of neonatal neurologic and respiratory problems with infant serum levels higher than 0.64 mEq/L [16]. Cases of neonatal hyperbilirubinemia, cardiac rhythm disturbances, hypothyroidism, and diabetes insipidus have been reported [16, 20]. In some cases, the maternal and/or neonatal serum lithium levels were above the therapeutic level, although complications have also been reported in the presence of relatively low infant serum levels. No cases of infant death have been reported in association with late pregnancy lithium exposure. Exposed newborns should be carefully monitored for potential complications, especially during the first 48 h.

Neurodevelopmental Effects

There is a paucity of data on the long-term effects of lithium on neurodevelopment, and it is often difficult to control for the effects of maternal mental illness. An observational retrospective cohort study of 15 children exposed to lithium in utero found that growth, behavior, and general development were normal when the children were evaluated at ages 3–15 years [21•]. Cognitive tests were also normal. Although most children had lower scores on the performance IQ subtest, this did not reach statistical significance. One child had signs of minor neurological dysfunction. Ten of the 30 children in the original cohort reportedly showed signs of neonatal toxicity, including respiratory symptoms, nausea and vomiting, hypoglycemia, hypotonia, and hyperbilirubinemia.

Therapeutic Drug Monitoring in Pregnancy and Postpartum

Maternal serum levels should be maintained in the therapeutic range during pregnancy. After establishing a pre-pregnancy baseline, we recommend checking levels monthly during pregnancy, unless clinically indicated to do so more often, as in women at high risk for dehydration, such as those with hyperemesis gravidarum [22••]. Lithium dose usually needs to be increased over the course of pregnancy, and we recommend that levels be checked weekly in the last month, both because of increased clearance rates and because of the potential for lithium toxicity in the presence of complications such as pre-eclampsia. A maternal lithium level should be checked upon presentation for delivery, and care should be taken to ensure adequate hydration. Non-steroidal anti-inflammatory and other nephrotoxic drugs should be avoided. As clearance decreases and fluid volume contracts following delivery, the lithium dose should be reduced immediately by 30–50 %. Lithium levels should be checked 24 h after delivery and after each dose adjustment [22••]. Discontinuation of lithium prior to or during delivery is not recommended in patients with therapeutic lithium levels [23].

Lactation

In a case series of 10 infants, maternal serum, milk, and infant serum levels were measured between 1 and 52 weeks postpartum [24]. The breast milk levels were about one half of the maternal serum levels, and the infant serum levels were then about one fourth of the maternal levels. Although all infants had normal TSH, BUN, and creatinine levels at birth, 1 infant developed an elevated TSH, 2 developed elevated BUN, and 1 an elevated creatinine. These changes resolved with cessation of nursing. In contrast, there is a case report of transient elevation of TSH which resolved while the infant continued to breastfeed on lithium [25]. In another case series, four infants who had been exposed to lithium throughout pregnancy and then breastfeeding (with or without other psychotropics) were found to have serum lithium levels that were only 10–17 % of maternal levels [26]. One of the four infants had fine and gross motor delays, but a second child born from the same mother, with the same exposures, had no developmental delays. We recommend monitoring the breastfed infants' lithium level, TSH, and renal function periodically.

Anticonvulsants

Valproic Acid

Congenital Malformations

Valproic acid has been associated with increased rates of congenital malformations and neurodevelopmental delays, particularly in comparison to other anticonvulsants. The majority of studies have been conducted in women with epilepsy. Valproic acid use during the first trimester has been associated with a 0.6 to 2 % incidence of neural tube defects, primarily lumbar meningomyelocele, and an increased rate of total congenital malformations [27, 28]. As an example, the rate of major malformations reported by the UK Epilepsy In Pregnancy Register was 6.2 % (based on 715 exposed pregnancies and 44 children with major malformations) [29]. The Neurodevelopmental Effects of Antiepileptic Drugs Study, which was conducted in the USA and the UK, reported a rate of 17.7 % based on 69 infants [30]. The North American Antiepileptic Drug (AED) Pregnancy Registry reported on the outcome of pregnancies enrolled between 1997 and 2011 [31]. The prevalence of malformations following first trimester exposure to valproate monotherapy was 9.3 % ($N = 323$), and the relative risk of malformations was 9.0 (95 % confidence interval 3.4–23.3) compared to an unexposed control group. Ninety-two percent of the women were taking anticonvulsants for epilepsy, 6 % for bipolar disorder, and 2 % for other conditions. Registry data are limited by the inability to include all exposed pregnancies. In comparison to lamotrigine-exposed pregnancies, the rate of malformations increased with increasing doses of valproate, and there was no threshold below which the rate was not increased. Other studies have also reported a positive dose-response relationship [29, 32–34]. A fetal valproate syndrome has been described and may include facial clefts, cardiac defects, limb defects, hypospadias, and abnormal facial features including a depressed nasal bridge, small nose, flat and long philtrum, a thin upper lip, and abnormal ears [35].

Neurodevelopmental Effects

Neurodevelopmental teratogenicity has been reported with exposure to valproic acid during pregnancy. A Danish study found that children whose mothers had filled a prescription for valproic acid during pregnancy were more likely to develop autism or an autism spectrum disorder than children whose mothers did not [36•]. For autism, the adjusted hazard ratio was 5.2 (95 % confidence interval 2.7–10) and for autism spectrum disorder, the adjusted hazard ratio was 2.9 (95 % confidence interval 1.7–4.9). Neither the timing of the exposure nor the dose affected the results. These results were also adjusted for parental psychiatric disorder (using registry-based diagnostic codes) and other potential confounds.

The FDA issued a warning in 2009 that valproic acid should be avoided in women of childbearing potential for non-life-threatening conditions including migraines and stated that "valproic acid should be used in pregnancy for epilepsy or bipolar disorder only when other treatments are not effective or not acceptable" [37]. The warning further advised that women should use an adequate method of contraception while taking valproic acid and encouraged women to enroll in the North American AED Pregnancy Registry if they became pregnant on valproic acid.

If valproic acid must be used in a woman of childbearing potential, we recommend documentation of the patient's history including response to prior medication trials, family history of response to medications when available, and the clinical presentation that justifies the use of this medication.

Lamotrigine

Congenital Malformations

Lamotrigine is an anticonvulsant approved for the treatment of bipolar depression and for maintenance therapy of bipolar disorder. The North American AED Drug Registry reported an increased risk for oral clefts (risk 4.5/1000, 95 % CI 2.0–8.8) [31] but other registries and studies have not replicated this finding. A European population-based case control study, which included 19 registries that surveyed 3.9 million births, reported a rate of isolated orofacial clefts with lamotrigine monotherapy of 0.47/1000 and an adjusted odds ratio of

0.67 compared to unexposed controls (95 % CI 0.10–2.34) [38]. The rate of total malformations has also been reported to be comparable to unexposed controls [31, 38, 39]. In a prospective study from the UK Epilepsy and Pregnancy Register, the rate of congenital malformations following lamotrigine monotherapy was 2.3 % (95 % CI 1.8–3.1 %), while the rate with valproic acid was three times higher [40]. No dose-response relationship was observed in this most recent report in contrast to previous reports from the Register.

Perinatal Complications and Pregnancy Outcomes

A study from the Norwegian Medical Birth Registry found no increased risk for fetal growth restriction in terms of head circumference or weight [41].

Neurodevelopmental Effects

The Neurodevelopmental Effects of Antiepileptic Drugs Study (NEAD) reported that children exposed to lamotrigine monotherapy had higher IQ and memory skills, verbal skills, and non-verbal skills at age 6 years in comparison to those exposed to valproic acid [42]. The average IQ was 108 (95 % CI 105–111, $N=73$) for the lamotrigine group, and there was no dose-response relationship for lamotrigine, in contrast to valproic acid. Likewise, there were no significant differences in the need for educational intervention or in full scale IQ scores between 6-year olds exposed to lamotrigine monotherapy in utero and the offspring of an unexposed control group whose mothers did not have epilepsy [43]. No increased risk for neurodevelopmental disorders at age 6 years was found in a group of children exposed to lamotrigine monotherapy compared to the unexposed offspring of a control group of women without epilepsy [44]. Some of the subjects in the two latter studies were included in the NEAD study. In the Norwegian Mother and Child Cohort Study (MoBa), maternal ratings for sentence skills and autistic traits at 36 months for children exposed to lamotrigine monotherapy ($N=44$) were worse than those of an unexposed control group [45]. Clinician ratings were not performed.

Placental Passage

A recent case series of six women treated with lamotrigine monotherapy or polytherapy for epilepsy and followed prospectively during pregnancy and delivery reported a poor correlation between lamotrigine dose and maternal serum levels, but a strong correlation between maternal serum levels, amniotic fluid levels, and cord serum levels [46•]. The ratio of cord serum to maternal serum ranged from 0.48 to 1.27 (mean 0.81, standard deviation 0.28), consistent with the results of an earlier study of 45 mother-infant pairs [47]. We have no data on the transfer of lamotrigine during the first trimester when there is little if any maternal blood flow to the placenta. These findings are relevant to the second and third trimester exposure only.

Therapeutic Drug Monitoring in Pregnancy and Postpartum

Rising estrogen levels during pregnancy are associated with increased glucuronidation resulting in a progressive increase in lamotrigine clearance. On average, a 250 % dose increase is needed to sustain therapeutic drug levels across pregnancy for women with epilepsy [48]. Within days of delivery, lamotrigine clearance diminishes, and plasma levels increase. Levels continue to increase throughout the first 2 to 3 postpartum weeks necessitating dose reduction to avoid toxicity [22••]. The American Academy of Neurology recommends monitoring of lamotrigine levels during pregnancy for women with epilepsy [49]. Lamotrigine dosing for bipolar disorder is usually guided by clinical response rather than serum levels. We recommend obtaining a preconception lamotrigine level to use as a guide for prophylactically increasing the dose during pregnancy [22••, 50]. If such a level is not available, clinicians should closely monitor clinical response and maintain a low threshold for increasing the lamotrigine dose [22••]. Some experts suggest that the level should be checked monthly [51]. We recommend tapering to the preconception dose over the first 2 weeks after delivery. However, if the pre-pregnancy dose was sub-therapeutic, we also recommend considering not lowering the dose by as much postpartum.

Lactation

The plasma lamotrigine level in breastfed infants has been reported to be as high as 18–50 % of the maternal levels (median 30 %) though no adverse events were reported [52, 53]. There are no reports of Stevens Johnson syndrome in babies exposed in utero or during lactation. There are several case reports of transient rashes during breastfeeding that resolved without discontinuing exposure to lamotrigine [54]. A report from the Norwegian MoBa study found no impact from breastfeeding during the first year on development at age 3 years [55]. A report from the NEAD Study showed no effect of exposure during breastfeeding on IQ at ages 3 and 6 years [56, 57]. An expert review concluded that the rate of adverse events during lactation was low, and that breastfeeding should be supported [58].

Lamotrigine and Oral Contraceptives

Data from both epilepsy patients and healthy control subjects indicate that oral contraceptives can increase the metabolism of lamotrigine, resulting in lower blood levels and decreased efficacy [59–61]. Conversely, stopping oral contraceptives

may lead to supra-therapeutic levels of lamotrigine with an attendant increase in side effects.

Folic Acid Supplementation

Given the high rate of unplanned pregnancies, supplementation with folic acid 4 mg/day is recommended for all women taking anticonvulsants whether or not they plan to become pregnant [18].

Antipsychotics

Newer antipsychotics including olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, lurasidone, and clozapine are increasingly used for the treatment of bipolar disorder. Most studies report combined data rather than presenting drug-specific information. Only one study attempted to control for confounding by indication [62].

Congenital Malformations

Data on pregnancy outcome after exposure to a combined group of newer antipsychotic drugs are available, although these data are not informative about possible effects of the individual medications. A prospective study from Canada evaluating newer antipsychotics in pregnancy was published in 2005 [63]. The study included the outcomes of 151 pregnancies exposed in the first trimester to olanzapine, $N=60$; risperidone, $N=49$; quetiapine, $N=36$; or clozapine, $N=6$. The rate of malformations in the exposed group was 0.9 % compared to 1.5 % in an unexposed control group.

A Swedish Medical Birth Register study reported that among 147 pregnancies with first trimester exposure to newer antipsychotics, the rate of major malformations was 4.1 % which was similar to the rate following exposure to older antipsychotics [64].

A prospective observational cohort study from a German teratology information service compared 561 pregnancies exposed mostly to olanzapine or quetiapine with 284 pregnancies with first trimester exposure to an older antipsychotic and to a control group of 1122 unexposed pregnancies [65]. Although there was no statistically significant difference in the rate of malformations between babies exposed to newer compared to older medications, there was an increased relative risk of malformation in babies exposed to newer drugs compared to the unexposed control group (adjusted odds ratio 2.17, 95 % confidence interval 1.20–3.91). The authors noted that this finding might be secondary to detection bias, as the most common malformations were cardiac malformations, mostly septal defects. Women taking antipsychotic drugs consumed more alcohol and cigarettes, had higher BMIs, had higher rates of unplanned pregnancies, had lower rates of folic acid use, and were more likely to be taking additional medications.

A study from The Australian National Register of Antipsychotic Medication in Pregnancy reported a malformation rate of 5.6 % among 142 livebirths with monotherapy or polytherapy exposure to newer antipsychotics, half of which were quetiapine ($N=74$) [66]. There was no unexposed control group.

According to a Danish review of the published literature through 2014 and of data from the Swedish Medical Birth Register, the rates of malformations following first trimester exposure to olanzapine ($N=1090$) or quetiapine ($N=443$) (as monotherapy or polytherapy) were 3.5 % and 3.6 % respectively, and were not significantly different from the background rate of malformations [67••].

Perinatal Complications

In the 2005 study from Canada, there were no differences in gestational age at birth or in the rate of miscarriages or stillbirths, but there was a higher incidence of low birth weight babies in a group exposed to newer antipsychotics (10 vs 2 %) [63]. In the German study, the rates of preterm birth in the newer antipsychotic group was similar to the unexposed control group, while the rate was higher in the group exposed to older antipsychotics (9.2 %, 8.7 %, and 15.7 % respectively) [65]. The rates of neonatal complications were elevated in both exposed groups compared to the unexposed controls (older drugs 21.6 %, newer drugs 15.6 %, and controls 4.2 %). The Australian registry study reported that 18 % of 142 babies were born preterm, and that 43 % required special care [66]. The concomitant use of mood stabilizers or high doses of antipsychotics increased this likelihood.

In 2015, a systematic review and meta-analysis of the outcomes associated with perinatal antipsychotic exposure from 13 cohort studies was published [68]. Antipsychotic exposure was associated with an increased risk of major malformations (with an absolute risk difference (ARD) of 0.03), heart defects (ARD 0.01), preterm delivery (ARD 0.05), smallness for gestational age (ARD 0.05), and decreased birth weight. There was no significant difference in teratogenic risk between older and newer antipsychotics. The authors stated that the data were not sufficient "to make any conclusions regarding the causal relationship between antipsychotic exposure and pregnancy outcomes."

A population-based cohort study from the Swedish Medical Birth Register reported an increased risk of gestational diabetes following exposure to an antipsychotic (adjusted OR 1.77, 95 % CI 1.04–3.03) [69].

In 2015, a population-based cohort study compared maternal and neonatal outcomes in a group of 1021 women taking an antipsychotic medication compared to an unexposed control group that was matched using high dimensional

propensity scoring to help adjust for confounding by indication [62]. There were no increased risks of gestational diabetes, gestational hypertension, venous thromboembolism, preterm birth, smallness for gestational age, largeness for gestational age, or poor neonatal adaptation in the exposed group. Most of the women were taking a newer antipsychotic, and over half were taking quetiapine.

An increased summary odds ratio for malformations (sOR 2.03, 95 % CI 1.41–2.93) and for preterm birth (sOR 1.85 (95 % CI 1.20–1.86) was reported in a 2015 meta-analysis for first trimester exposure to newer antipsychotics compared to unexposed controls [70]. The results for malformations reflect the largest study included [65]. This study combined multiple medications and did not adjust for confounding by indication.

In 2011, the FDA updated the pregnancy section of the labeling for all antipsychotic drugs regarding a risk of neonatal complications following the third trimester exposure [71]. Neonatal complications included extrapyramidal signs, tremor, abnormally increased or decreased muscle tone, breathing and feeding difficulties, sedation, and agitation. These complications may resolve spontaneously or may require additional hospital care.

Neurodevelopment

In a small US study of 22 mother-infant pairs exposed to older and newer antipsychotics, scores on an infant development scale were lower than in a control group of the offspring of women who did not take antipsychotics, but the scores also correlated with the severity of maternal illness [72]. The majority of women in both groups took other psychotropic medications excluding anticonvulsants. In a study from China, 76 infants of mothers with schizophrenia who had taken a newer antipsychotic during pregnancy were compared to an unexposed control group of 76 mother-infant pairs unexposed to illness or medication [73]. There were no malformations reported, and there was no difference in mean birth weight or gestational age. More antipsychotic-exposed infants met criteria for delayed development at 2 months than the controls, but there were no differences at 12 months. Women in the exposed group were less likely to take prenatal vitamins, more likely to be overweight, and less likely to breastfeed. The study did not adjust for tobacco and alcohol use among other confounds.

Placental Transfer

Quetiapine has the lowest rate of placental transfer (23.8 %) compared to the rates for olanzapine (72.1 %) and risperidone (49.2 %) [74]. This information pertains to the second and third trimesters.

Pharmacokinetics

Antipsychotic metabolism can change during pregnancy, so close monitoring is recommended, with dose adjustments as clinically indicated [22••].

Lactation

The data for antipsychotics is limited to case reports. Exposure during pregnancy is greater than in breastfeeding so continuing the original medication is recommended.

Summary on Antipsychotics

As the potential for weight gain with olanzapine is greater and there is a higher risk of hyperprolactinemia with risperidone, we recommend quetiapine as the first-line antipsychotic in a woman trying to conceive. The choice of psychotropics in pregnancy depends upon the clinical circumstances.

Pregnancy Registries

Women taking anticonvulsants or antipsychotics during pregnancy may be enrolled in the following registries:

1. North American Antiepileptic Drug (AED) Pregnancy Registry: http://www.massgeneral.org/aed/
2. Europe and other continents: EURAP Registry (International Registry of Antiepileptic Drugs and Pregnancy): http://www.eurapinternational.org/about/join
3. National Pregnancy Registry for Atypical Antipsychotics (unexposed women may also enroll as controls): http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/atypicalantipsychotic/

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is a treatment option for pregnant patients with severe mental illness. Conditions treated have included severe depression, mania, and psychosis, especially if there is a high risk for suicide, violence, catatonia, or neuroleptic malignant syndrome [15, 75]. ECT should be considered when acute treatment is needed, particularly in the setting of severe dehydration and malnutrition, and when the patient refuses medication or fails to respond to it. Reviews of cases published from 1941 to 2009 concluded that the risks of adverse events in the gravida and the fetus were low [76, 77]. A 2015 review of reports in the literature from 1942 to 2013 found that there were 169 cases for which primary data were available, while previous reviews had considered primary cases and secondary reports [78]. After combining the diverse

cases to calculate rates of adverse events, the authors concluded that ECT carried significant risks for the fetus; however, case reports are subject to reporting bias and do not represent all patients who were treated, especially those treated successfully. Combining them gives an inaccurate picture, and relative risk cannot be calculated without denominator-based studies. We, along with other experts, consider ECT an option in pregnancy with modifications in technique to minimize complications for the gravida and the fetus [15, 75].

Conclusion

The management of women with bipolar disorder presents challenges in pregnancy and postpartum. Given the high rate of unplanned pregnancies, the time to start planning is when a woman of reproductive age first presents for psychiatric care. The postpartum period is a time of increased risk for new-onset mental illness, and postpartum psychosis may be the first episode of a bipolar disorder. Screening for bipolar disorder will reduce the chances that the patient will be misdiagnosed with unipolar depression and treated with antidepressant monotherapy. We recommend holding an informed consent discussion regarding pregnancy and lactation as early in the treatment course as possible, according to clinical considerations. Discontinuing or reducing medication can convert the stable patient to an unstable patient. The changes in drug metabolism during pregnancy can also lead to destabilization by reducing the effective drug level. In order to prevent or attenuate this risk of relapse, it is imperative that pregnant patients are evaluated carefully and monitored closely throughout pregnancy and in the first year postpartum.

We have reviewed the use of lithium, lamotrigine, valproic acid, newer antipsychotics, and ECT. Valproic acid should only be used if other treatment options are ineffective or if the risk of discontinuing it is too high, and the rationale for its use should be documented. Adequate control of the mood disorder is of paramount importance, with treatment choices made to provide the greatest benefit to the mother and child while minimizing the potential risks.

Compliance with Ethical Standards

Conflict of Interest Sabrina J. Khan, Madeleine E. Fersh, Carrie Ernst, Kim Klipstein, and Elizabeth Streicker Albertini declare that they have no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the postpartum period. Lancet. 2014;384(9956):1789–99. doi:10.1016/s0140-6736(14)61278-2.
2. Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, et al. The impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry. 2002;63(4):284–7.
3. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry. 2007;164(12):1817–24. doi:10.1176/appi.ajp.2007.06101639.
4. Sharma V, Burt VK, Ritchie HL. Bipolar II postpartum depression: detection, diagnosis, and treatment. Am J Psychiatry. 2009;166(11):1217–21. doi:10.1176/appi.ajp.2009.08121902.
5. Frey BN, Simpson W, Wright L, Steiner M. Sensitivity and specificity of the Mood Disorder Questionnaire as a screening tool for bipolar disorder during pregnancy and the postpartum period. J Clin Psychiatry. 2012;73(11):1456–61. doi:10.4088/JCP.12m07856.
6. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118 Suppl 1:1–203. doi:10.1111/j.1471-0528.2010.02847.x.
7. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry. 2000;157(2):179–84.
8. Bergink V, Armangue T, Titulaer MJ, Markx S, Dalmau J, Kushner SA. Autoimmune encephalitis in postpartum psychosis. Am J Psychiatry. 2015:appiajp201514101332. doi:10.1176/appi.ajp.2015.14101332.
9. Merrill L, Mittal L, Nicoloro J, Caiozzo C, Maciejewski PK, Miller LJ. Screening for bipolar disorder during pregnancy. Arch Womens Ment Health. 2015;18(4):579–83. doi:10.1007/s00737-015-0527-y.
10. Chessick CA, Dimidjian S. Screening for bipolar disorder during pregnancy and the postpartum period. Arch Womens Ment Health. 2010;13(3):233–48. doi:10.1007/s00737-010-0151-9.
11. Sharma V, Xie B. Screening for postpartum bipolar disorder: validation of the Mood Disorder Questionnaire. J Affect Disord. 2011;131(1–3):408–11. doi:10.1016/j.jad.2010.11.026.
12. Sharma V, Pope CJ. Pregnancy and bipolar disorder: a systematic review. J Clin Psychiatry. 2012;73(11):1447–55. doi:10.4088/JCP.11r07499.
13. March of Dimes Foundation. Quick facts: birth defects. 2013 [8/5/15]; Available from: http://www.marchofdimes.com/peristats/ViewTopic.aspx?reg=99&top=16&lev=0&slev=1&dv=mt.
14. Boden R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ. 2012;345, e7085. doi:10.1136/bmj.e7085.

15. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, et al. Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry. 2004;161(4):608–20.
16. Newport DJ, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. Am J Psychiatr. 2005;162(11):2162–70.
17. Nora JJ, Nora AH, Toews WH. Letter: Lithium, Ebstein's anomaly, and other congenital heart defects. Lancet. 1974;2(7880):594–5.
18. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium.[see comment][erratum appears in JAMA 1994 May 18;271(19): 1485]. JAMA. 1994;271(2):146–50.
19.•• Diav-Citrin O, Shechtman S, Tahover E, Finkel-Pekarsky V, Arnon J, Kennedy D, et al. Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. Am J Psychiatry. 2014;171(7):785–94. doi:10.1176/appi.ajp.2014.12111402. **This is a prospective, comparative observational study evaluating the risk of major malformations associated with lithium exposure during pregnancy. Lithium exposure was associated with an increased rate of cardiovascular anomalies (5/123 [4.1%] compared with 4/711 [0.6%] in the non-teratogenic exposure group), however this risk was no longer statistically significant after excluding malformations which resolved spontaneously.**
20. Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: another clinical report and a review of the literature. Am J Med Genet A. 2005;132A(4): 441–4. doi:10.1002/ajmg.a.30501.
21.• van der Lugt NM, van de Maat JS, van Kamp IL, Knoppert-van der Klein EA, Hovens JG, Walther FJ. Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies. Early Hum Dev. 2012;88(6):375–8. doi:10.1016/j.earlhumdev.2011.09.013. **This observational retrospective cohort study evaluated the growth and neurodevelopment of 15 children exposed to lithium in pregnancy at 3–15 years and found that lithium exposure was not associated with adverse effects on growth and cognitive development.**
22.•• Deligiannidis KM, Byatt N, Freeman MP. Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. J Clin Psychopharmacol. 2014;34(2):244–55. doi:10.1097/jcp.0000000000000087. **This paper reviews the pharmacokinetic changes of antidepressants and mood stabilizers during pregnancy, discusses the implications for clinical and therapeutic drug monitoring, and offers clinical recommendations.**
23. Bergink V, Kushner SA. Lithium during pregnancy. Am J Psychiatry. 2014;171(7):712–5. doi:10.1176/appi.ajp.2014.14030409.
24. Viguera AC, Newport D, Ritchie J, Stowe Z, Whitfield T, Mogielnicki J, et al. Lithium in breast milk and nursing infants: clinical implications. Am J Psychiatry. 2007;164(2):342–5.
25. Marin Gabriel MA, Olza Fernandez I, Donoso E, Gutierrez Cruz N. Lithium and artificial breastmilk; or is maternal breastfeeding better? An Pediatr (Barc). 2011;75(1):67–8. doi:10.1016/j.anpedi.2010.12.007.
26. Bogen DL, Sit D, Genovese A, Wisner KL. Three cases of lithium exposure and exclusive breastfeeding. Arch Womens Ment Health. 2012;15(1):69–72. doi:10.1007/s00737-012-0257-3.
27. Tomson T, Battino D. Antiepileptic treatment in pregnant women: morphological and behavioural effects. Handb Exp Pharmacol. 2011;205:295–315. doi:10.1007/978-3-642-20195-0_15.
28. Werler MM, Ahrens KA, Bosco JL, Mitchell AA, Anderka MT, Gilboa SM, et al. Use of antiepileptic medications in pregnancy in relation to risks of birth defects. Ann Epidemiol. 2011;21(11):842–50. doi:10.1016/j.annepidem.2011.08.002.
29. Mawhinney E, Campbell J, Craig J, Russell A, Smithson W, Parsons L, et al. Valproate and the risk for congenital malformations: is formulation and dosage regime important? Seizure. 2012;21(3):215–8. doi:10.1016/j.seizure.2012.01.005.
30. Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, Mawer G, Pennell PB, Smith JC, Wolff MC, Group NS. In utero antiepileptic drug exposure: fetal death and malformations.[see comment]. Neurology. 2006;67(3):407–12.
31. Hernandez-Diaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012;78(21):1692–9. doi:10.1212/WNL.0b013e3182574f39.
32. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate: evidence of dose relationship in teratogenic effect. CNS Drugs. 2008;22(4):325–34.
33. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011;10(7):609–17. doi:10.1016/S1474-4422(11)70107-7.
34. Vajda FJ, O'Brien TJ, Graham JE, Lander CM, Eadie MJ. Dose dependence of fetal malformations associated with valproate. Neurology. 2013;81(11):999–1003. doi:10.1212/WNL.0b013e3182a43e81.
35. Ozkan H, Cetinkaya M, Koksal N, Yapici S. Severe fetal valproate syndrome: combination of complex cardiac defect, multicystic dysplastic kidney, and trigonocephaly. J Matern Fetal Neonatal Med. 2011;24(3):521–4. doi:10.3109/14767058.2010.501120.
36.• Christensen J, Gronborg TK, Sorensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309(16): 1696–703. doi:10.1001/jama.2013.2270. **This Danish population based study found that prenatal exposure to valproate was associated with an increased risk of autism spectrum disorder and childhood autism; the 508 children exposed to valproate had an absolute risk of 4.42 % (95 % CI, 2.59–7.46 %) for autism spectrum disorder (adjusted HR, 2.9 [95 % CI, 1.7–4.9]) and an absolute risk of 2.50 % (95 % CI, 1.30–4.81 %) for childhood autism (adjusted HR, 5.2 [95 % CI, 2.7–10.0])**.
37. FDA. Valproate sodium and related products (valproic acid and divalproex sodium): risk of birth defects: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192788.htm [released 12/3/09]. 2009 [8/14/15].
38. Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology. 2008;71(10):714–22.
39. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA. 2011;305(19): 1996–2002. doi:10.1001/jama.2011.624.
40. Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry. 2014;85(9):1029–34. doi:10.1136/jnnp-2013-306318.
41. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol. 2014;261(3):579–88. doi:10.1007/s00415-013-7239-x.
42. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective

observational study. Lancet Neurol. 2013;12(3):244–52. doi:10.1016/s1474-4422(12)70323-x.

43. Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, Garcia-Finana M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology. 2015;84(4):382–90. doi:10.1212/wnl.0000000000001182.
44. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014;10, Cd010236. doi:10.1002/14651858.CD010236.pub2.
45. Veiby G, Daltveit AK, Schjolberg S, Stoltenberg C, Oyen AS, Vollset SE, et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. Epilepsia. 2013;54(8):1462–72. doi:10.1111/epi.12226.
46.• Paulzen M, Lammertz SE, Veselinovic T, Goecke TW, Hiemke C, Grunder G. Lamotrigine in pregnancy—therapeutic drug monitoring in maternal blood, amniotic fluid, and cord blood. Int Clin Psychopharmacol. 2015;30(5):249–54. doi:10.1097/yic.0000000000000088. **This study measured lamotrigine concentrations in maternal blood, amniotic fluid, and umbilical cord blood in six mother-infant pairs at delivery. Lamotrigine levels in serum were strongly correlated with the lamotrigine levels in the amniotic fluid and cord blood.**
47. Kacirova I, Grundmann M, Brozmanova H. Serum levels of lamotrigine during delivery in mothers and their infants. Epilepsy Res. 2010;91(2–3):161–5. doi:10.1016/j.eplepsyres.2010.07.007.
48. Fotopoulou C, Kretz R, Bauer S, Schefold JC, Schmitz B, Dudenhausen J, et al. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. Epilepsy Res. 2009;85(1):60–4.
49. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73(2):142–9. doi:10.1212/WNL.0b013e3181a6b325.
50. Newport DJ, Stowe ZN, Viguera AC, Calamaras MR, Juric S, Knight B, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disord. 2008;10(3):432–6. doi:10.1111/j.1399-5618.2007.00565.x.
51. Clark CT, Klein AM, Perel JM, Helsel J, Wisner KL. Lamotrigine dosing for pregnant patients with bipolar disorder. Am J Psychiatry. 2013;170(11):1240–7. doi:10.1176/appi.ajp.2013.13010006.
52. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia. 2000;41(6):709–13.
53. Page-Sharp M, Kristensen JH, Hackett LP, Beran RG, Rampono J, Hale TW, et al. Transfer of lamotrigine into breast milk. Ann Pharmacother. 2006;40(7–8):1470–1.
54. Wakil L, Epperson CN, Gonzalez J, O'Reardon JP, Kim DR. Neonatal outcomes with the use of lamotrigine for bipolar disorder in pregnancy and breastfeeding: a case series and review of the literature. Psychopharmacol Bull. 2009;42(3):91–8.
55. Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. JAMA Neurol. 2013;70(11):1367–74. doi:10.1001/jamaneurol.2013.4290.
56. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. Neurology. 2010;75(22):1954–60. doi:10.1212/WNL.0b013e3181ffe4a9.
57. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr. 2014;168(8):729–36. doi:10.1001/jamapediatrics.2014.118.
58. Veiby G, Bjork M, Engelsen BA, Gilhus NE. Epilepsy and recommendations for breastfeeding. Seizure. 2015;28:57–65. doi:10.1016/j.seizure.2015.02.013.
59. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res. 2001;47(1–2):151–4.
60. Sabers A, Ohman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. Neurology. 2003;61(4):570–1.
61. Christensen J, Petrenaite V, Atterman J, Sidenius P, Ohman I, Tomson T, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. Epilepsia. 2007;48(3):484–9. doi:10.1111/j.1528-1167.2007.00997.x.
62. Vigod SN, Gomes T, Wilton AS, Taylor VH, Ray JG. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. BMJ. 2015;350:h2298. doi:10.1136/bmj.h2298.
63. McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, Levinson A, Zipursky RB, Einarson A. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study.[see comment]. Journal of Clinical Psychiatry. 2005;66(4):444–9; quiz 546.
64. Reis M, Kallen B. Maternal use of antipsychotics in early pregnancy and delivery outcome. J Clin Psychopharmacol. 2008;28(3):279–88. doi:10.1097/JCP.0b013e318172b8d5.
65. Habermann F, Fritzsche J, Fuhlbruck F, Wacker E, Allignol A, Weber-Schoendorfer C, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. J Clin Psychopharmacol. 2013;33(4):453–62. doi:10.1097/JCP.0b013e318295fe12.
66. Kulkarni J, Worsley R, Gilbert H, Gavrilidis E, Van Rheenen TE, Wang W, et al. A prospective cohort study of antipsychotic medications in pregnancy: the first 147 pregnancies and 100 one year old babies. PLoS One. 2014;9(5), e94788. doi:10.1371/journal.pone.0094788.
67.•• Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. Basic Clin Pharmacol Toxicol. 2014. doi:10.1111/bcpt.12372. **A literature review of the available data on the risk of malformations with first-trimester exposure to the newer antipsychotics: olanzapine, quetiapine, risperidone and aripiprazole. The rate of malformation was 3.5 % for olanzapine, 3.6 % with quetiapine, and 5.1 % with risperidone; data for aripiprazole was limited.**
68. Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. Obstet Gynecol. 2015;125(5):1224–35. doi:10.1097/aog.0000000000000759.
69. Boden R, Lundgren M, Brandt L, Reutfors J, Kieler H. Antipsychotics during pregnancy: relation to fetal and maternal metabolic effects. Arch Gen Psychiatry. 2012;69(7):715–21. doi:10.1001/archgenpsychiatry.2011.1870.
70. Terrana N, Koren G, Pivovarov J, Etwel F, Nulman I. Pregnancy outcomes following in utero exposure to second-generation antipsychotics: a systematic review and meta-analysis. J Clin Psychopharmacol. 2015;35(5):559–65. doi:10.1097/JCP.0000000000000391.
71. FDA. FDA Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns: http://www.

fda.gov/Drugs/DrugSafety/ucm243903.htm [released 2/22/2011]. 2011 [8/14/15].
72. Johnson KC, LaPrairie JL, Brennan PA, Stowe ZN, Newport DJ. Prenatal antipsychotic exposure and neuromotor performance during infancy. Arch Gen Psychiatry. 2012;69(8):787–94. doi:10.1001/archgenpsychiatry.2012.160.
73. Peng M, Gao K, Ding Y, Ou J, Calabrese JR, Wu R, et al. Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. Psychopharmacology (Berlin). 2013. doi:10.1007/s00213-013-3060-6.
74. Newport DJ, Calamaras MR, DeVane CL, Donovan J, Beach AJ, Winn S, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry. 2007;164(8):1214–20.
75. Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Obstet Gynecol. 2009;114(3):703–13. doi:10.1097/AOG.0b013e3181ba0632.
76. Miller LJ. Use of electroconvulsive therapy during pregnancy. Hosp Commun Psychiatry. 1994;45(May):444–50.
77. Anderson EL, Reti IM. ECT in pregnancy: a review of the literature from 1941 to 2007. Psychosom Med. 2009;71(2):235–42. doi:10.1097/PSY.0b013e318190d7ca.
78. Leiknes KA, Cooke MJ, Jarosch-von Schweder L, Harboe I, Hoie B. Electroconvulsive therapy during pregnancy: a systematic review of case studies. Arch Womens Ment Health. 2015;18(1):1–39. doi:10.1007/s00737-013-0389-0.