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REVIEW ARTICLE

Depression during pregnancy: detection, comorbidity and treatment

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Abstract
Depression during pregnancy is common (~15%). Routine prenatal depression screening coupled with the use of physician collaborators to assist in connecting women with care is critical to facilitate treatment engagement with appropriate providers. Providers should be aware of risk factors for depression – including a previous history of depression, life events, and interpersonal conflict – and should appropriately screen for such conditions. Depression during pregnancy has been associated with poor pregnancy outcomes including preeclampsia, insufficient weight gain, decreased compliance with prenatal care, and premature labor. Current research has questioned the overall benefit of treating depression during pregnancy with antidepressants when compared to the risk of untreated depression for mother and child. Published guidelines favor psychotherapy above medication as the first line treatment for prenatal depression. Poor neonatal adaptation or withdrawal symptoms in the neonate may occur with fetal exposure in late pregnancy, but the symptoms are mild to moderate and transient. The majority of mothers who decide to stop taking their antidepressants during pregnancy suffer relapsing symptoms. If depression continues postpartum, there is an increased risk of poor mother–infant attachment, delayed cognitive and linguistic skills in the infant, impaired emotional development, and behavioral problems in later life. Bipolar depression, anxiety and substance use disorders, and/or presence of severe psychosocial stress can lead to treatment-resistance. Modified and more complex treatment algorithms are then warranted. Psychiatric medications, interpersonal or cognitive-behavioral therapy, and adjunctive parent–infant/family treatment, as well as social work support, are modalities often required to comprehensively address all issues surrounding the illness.

Prevalence, symptoms, and predisposing factors of depression

Depressive symptoms present in up to 20% of women, commonly occuring during childbearing years (Weissman & Olfson, 1995). Studies show that 10–16% of pregnant women meet the diagnostic criteria for major depressive disorder (MDD), with greater numbers suffering from subsyndromal illness (O'Hara *et al*. 1984). However, even when appropriately screened, over 80% of women with antenatal depression do not receive treatment during pregnancy (Marcus *et al*. 2003). Frequently cited reasons for undertreatment are concerns regarding stigma (Roeloffs *et al*. 2003), or diagnostic uncertainty among professionals confusing depressive syndromatology with normative pregnancy experiences (poor sleep, fatigue, appetite dysregulation). Effective treatment is also sometimes limited by underdosing of otherwise effective medications because many physicians are unsure how to balance maternal medication with the risk of exposing the growing fetus to pharmacotherapy. Finally, even if treated aggressively, depression during pregnancy may prove treatment-refractory due to secondary maintaining factors including the presence of bipolar depression, anxiety disorders, substance abuse, or the presence of severe psychosocial stressors.

Depression during childbearing presents with the same symptomatology as depressive episodes outside of childbearing. According to the *Diagnostic and*

Statistical Manual of Mental Disorders, Version 4 (DSM-IV) criteria, a diagnosis of depression must include existence of a depressed mood or inability to experience pleasure (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. 2000); many women who are depressed during the puerperium also note an irritable mood and marked anxiety as key features. Frequently women report worrisome cognitions regarding the infant's health and preoccupations about becoming a competent parent. These preoccupations can take on an obsessional flavor and in a few cases deteriorate to psychotic thinking. Many of the classic symptoms of depression (sleep and appetite dysregulation, poor energy) overlap with the physical and mental changes experienced during pregnancy, often resulting in them being misattributed to the physiologic changes during gestation.

Practitioners caring for women should be aware of personal and epidemiologic factors that place women at the greatest risk for antenatal depression. A critical primary risk factor is genetic vulnerability manifesting as previous personal depression or family history (particularly during pregnancy or postpartum) of depression (O'Hara *et al*. 1984). Other common risk factors are a woman's perception of limited social support and presence of social conflict, which may be red flags suggesting that those women might benefit from a clinical intervention (Westdahl *et al*. 2007). Other risk factors include: past or present physical, emotional, or sexual abuse; current or past cigarette smoking; alcohol or substance abuse; financial or occupational stressors; medical health concerns; living alone; greater number of children at home; and finally, ambivalence about the pregnancy (Altshuler *et al*. 1998).

Screening and collaborative care

There are several user-friendly screening tools for depression that can be easily administered during pregnancy. The Edinburgh Postnatal Depression Scale (EPDS) is a brief 3-minute screening tool, initially developed for specific use in postpartum women (Cox *et al*. 1987), and is now the gold-standard instrument used across the peripartum. Two other commonly used depression screening measures for adults in ambulatory care are the Beck Depression Inventory Scale (BDI-II) (Feinman *et al*. 2000) and the Center for Epidemiologic Studies Depression Scale, Revised (CES-DR) (Radloff, 1977), both of which are valid for pregnancy use.

However, when using the BDI-II or the CES-DR clinicians have to consider the possibility of overdiagnosing depression because both instruments include items inquiring somatic complaints of depression which, in fact, could be pregnancy-related somatic experiences (e.g., fatigue or sleep disturbance due to urinary frequency or abdominal discomfort). Similarly, items assessing anhedonia, such as "I have enjoyed reading a book or watching TV," or psychomotor retardation, such as "I feel I am slowed down," are potentially more likely related to body changes due to pregnancy and following childbearing than due to depression. These concerns have lead to the development of the EPDS, a peripartum-specific depression measure validated for the use in pregnancy (Murray & Cox, 1990) and postpartum (Cox *et al*. 1987). Adaptations made by the EPDS include elimination of misleading or inappropriate items such as questions about weight change, body image change, somatic preoccupation, and work difficulty, and emphasis on more prototypical depression symptoms during the peripartum such as agitation, irritability and anxious preoccupation.

Regardless of the screening method used, it is important to further support patients who manifest depressive symptoms upon screening in their help seeking. Prior work suggests that only 14% of pregnant women screened in an obstetrics setting who report significant depressive symptoms seek any form of treatment (Marcus *et al*. 2003). Thus, obstetrics practices may benefit from nursing or care management services to facilitate treatment engagement in women with multiple stressors who screen positive for depression, as these women may be reluctant to seek appropriate treatment. Because management of a depressed, pregnant woman may be diagnostically complex and also includes care of her growing fetus, treatment may be optimized by applying an informed, multidisciplinary approach, that is, a collaborative care model, including input from an obstetrician, psychiatrist, pediatrician, and care manager to provide optimal care.

Consequences of antenatal depression

Unidentified and untreated depression can lead to detrimental effects in both the mother and her child. Maternal infanticide and/or suicide are the most catastrophic effects of undertreated depression (Meyer & Oberman, 2001). In addition, depressed women are more likely to participate in unhealthy practices during pregnancy such as smoking and substance use. They may have poor nutrition, in part due to lack of appetite, leading to poor pregnancy weight gain. Depressed women are less compliant with prenatal care and feel less invested in antenatal care. Women

with depression may have increased pain and discomfort during their pregnancies, often complaining of myriad somatic concerns, sometimes leading to medical procedures.

Untreated maternal depression during pregnancy has been associated with poor obstetric, fetal, and neonatal outcomes (Alder *et al*. 2007). Research suggests that maternal depression leads to an alteration in the mother's neuroendocrine axis and uterine blood flow, which may contribute to adverse pregnancy and infant outcomes. (Davis *et al*. 2007).

Research suggests that maternal depression leads to alteration in a mother's neuroendocrine axis and uterine blood flow, which may contribute to premature delivery, low birth weight, and preeclampsia (Wadhwa *et al*. 2009; Teixeira *et al*. 1999). Negative birth outcomes are associated most highly with depression symptoms in the second and third trimesters (Hoffman & Hatch, 2000). Babies of mothers who suffered from depression during their pregnancy have elevated cortisol and catecholamine levels at birth (ACOG Practice Bulletin 2008). These infants cry more often and are more difficult to console than babies born to non-depressed mothers (Zuckerman et al. 1990; Misri *et al*. 2004). Prenatal stress has been also found a reliable predictor of subsequent infant sleep (Heringhausen *et al*. 2008) and overall developmental and behavioral disturbances (Talge *et al*. 2007). Higher levels of prenatal maternal anxiety and depression predict more infant sleep problems at 18 and 30 months controlling for obstetric and psychosocial risk, as well as postpartum psychopathology (O'Connor *et al*. 2007). Other groups also reported on offspring behavioral problems in early and middle childhood (O'Conner *et al*. 2002; Van den Bergh and Marcoen, 2004), and in teenage years (Pawlby *et al*. 2009) when mothers were depressed/anxious/stressed during pregnancy. In addition, if untreated antenatal depression continues into the postpartum period, the risk for long-term effects on a child, such as poor mother-infant attachment, delayed cognitive and linguistic skills, impaired emotional development, and behavioral issues, exist (Forman *et al*. 2007; Coghil *et al*. 1986; Alpern & Lyons-Ruth, 1993; Bifulco *et al*. 2004). Studies show these babies are fussier, vocalize their needs less, and make fewer positive facial expressions than infants of non-depressed mothers (Field, 1995). If a baby is exposed to a depressed maternal environment during early infancy, and the mother has recurrent depressive episodes, the child shows changes in neuroendocrine functioning and more behavior problems at school entry (Essex *et al*. 2001). As these children grow, perhaps because of early exposure or the continued stressful home environment, they are more likely to have emotional instability and conduct disorders, attempt suicide, and require mental health services themselves (Lyons-Ruth *et al*. 2000; Weissman *et al*. 1984).

Comorbidity and other factors impacting treatment

Undiagnosed bipolar depression, comorbidity with other mental illness including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and co-occurring severe psychosocial stress can all contribute to treatment-resistance despite adequate treatment with antidepressants. Clinicians wanting to prevent treatment refractory states during pregnancy

Table 1. Key points for clinical care of treatment – refractory depression during pregnancy

Bipolar depression	Any woman who experiences significant irritability and a ''roughening'' course of her depressive illness during pregnancy or postpartum, particularly with psychotic features, should be evaluated for bipolar depression • A history of mood instability and more specifically the induction of hypomania, rapid cycling or mixed episodes, following treatment with antidepressants may provide a clue about the underlying bipolar nature • Poor or failed response to antidepressants and severe psychotic features also hint to underlying bipolar illness • A personal past history of postpartum depression or family history of bipolar illness also may suggest bipolar illness
Anxiety	Anxiety is common during pregnancy, ranging from increased rates of GAD and OCD, to possible exaggeration in panic disorder and PTSD • Comorbidity with depression is common, and co-occurrence of anxiety and depression complicates treatment hence increasing the risk of treatment-resistance
Substance use disorders	Substance use is frequently comorbid with anxiety and mood disorders, and may contribute to treatment-resistance if unrecognized and untreated • Patients frequently self-medicate with alcohol or other illicit drugs to alleviate anxiety, depression, or insomnia • Screening for substance abuse during pregnancy, mainly alcohol consumption, is critical for optimal child outcomes, and several screening tools are available in primary care

GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress syndrome.

need to consider these contributing factors and address them aggressively (Table 1).

Bipolar depression

Several factors, such as worsening dysphoria on selective serotonin reuptake inhibitors (SSRIs), agitation and extreme insomnia, and emerging psychosis should alert a clinician to a potential underlying bipolar depression. Bipolar illness is a severe recurrent illness, with a lifetime prevalence of between 1–2%, without gender specificity (Kessler *et al*. 1994). For patients who present for the first time during pregnancy, a differential diagnosis including infectious, immunologic, electrolyte or endocrine disorders should be considered. Medications which may contribute to affective roughening include steroids, bronchodilators, decongestants, antihypertensives, and immunosuppresants; but "unopposed" antidepressant medication alone can also trigger (hypo)mania and treatment refractoriness (Sharma, 2006).

Exacerbation of bipolar illness may be particularly problematic during pregnancy, as risk-taking behavior, including sexually promiscuous behavior and excessive use of drugs or alcohol, may put a fetus at risk. Overall, there is limited information about the course of bipolar illness during pregnancy (Sharma, 2009), whereas exacerbation of bipolar illness in postpartum is well documented. Recent studies suggest the risk of recurrence during pregnancy in preexisting bipolar illness is greater than 60% particularly when medication was discontinued (Viguera *et al*. 2000). Because many of the mood stabilizers may cause an increase in fetal anomalies when used during the first trimester, these medications are often tapered antepartum, leaving women vulnerable to exacerbations within the second and third trimester.

Anxiety disorders

Modest levels of anxiety occur in a majority of women during pregnancy, hence differentiating generalized anxiety disorder (GAD) can be difficult. GAD characterized by the presence of at least 6 months of excessive worry with additional unique somatic symptoms occurs at the rate of 8.5% during the last trimester of pregnancy. This rate exceeds the prevalence rate in nonpregnant samples (~3%), suggesting that peripartum is a vulnerable period for GAD (Ross *et al*. 2006). Prevalence of panic disorder during pregnancy is 1–2%, consistent with prevalence outside of childbearing. Current studies reveal conflicting data regarding the course of illness across peripartum. Several studies suggest that panic symptoms improve during pregnancy and exacerbate postpartum, while others note no change in the course of illness across the puerperium (Ross *et al*. 2006). Co-occurring anxiety and depressive systems are common in that 50% of women with panic disorders report major depression. This comorbidity may complicate treatment regimens and may necessitate the use of both an antidepressant and an anxiolytic (commonly SSRIs and benzodiazepines). Obsessive worries centering on pregnancy outcomes are very common during pregnancy. However, the prevalence of obsessive-compulsive disorder (OCD) is lower during pregnancy (0.2%) relative to both postpartum prevalence (2.7–3.9%) and lifetime prevalence in the general population (2.5%) (Ross *et al*. 2006). One of the most common obsessional themes during pregnancy is the fear of intentionally or accidentally harming the fetus, or that the fetus may have some undetected medical condition. Obsessive thoughts about harming the fetus (e.g., falling down stairs and hurting the unborn) must be differentiated from psychotic delusions present in psychotic depression or bipolar illness (e.g., delusion that fetus is "eating her up from the inside"). In general, women with OCD-like thoughts about hurting their child are very distressed, identifying these thoughts as unwanted and unreasonable. In contrast, women with psychotic harmful thoughts towards their child lack insight into their delusions and may be at risk of acting on their delusion (e.g., stabbing the fetus causing major abdominal injuries to herself). In such cases, imminent safety measures for the mother and child are warranted and necessitate emergent treatment of the mother. Presence of OCD spectrum disorders, comorbid with antenatal depression, complicates treatment and may require higher levels of medications (SSRIs) or behavioral therapy. Finally, post-traumatic stress disorder (PTSD) can be present during pregnancy, either as new onset or exacerbation of preexisting illness (Ross *et al*. 2006). In general, PTSD is approximately twice as common in women (12% lifetime prevalence) than in men. Prevalence rates among pregnant women are as high as 8%. PTSD symptoms have also been described in women who have experienced prior losses during pregnancy as well as those who have had prior complicated deliveries. History of childhood abuse, particularly sexual abuse, is related to higher rates of perinatal PTSD as well, with symptoms sometimes precipitated by the intrusive procedures inherent in the management of pregnancy and delivery. Childhood sexual abuse survivors are also more likely to suffer perinatal depression, confirming the observation that PTSD and depression are commonly comorbid during the perinatal period, again

complicating treatment algorithms and increasing the likelihood of treatment resistance.

Substance use disorders

Patients present, not infrequently, with preexisting comorbid substance abuse (alcohol and marijuana). Self-medication for mood and anxiety disorders is common (Bolton *et al*. 2009), (Robinson *et al*. 2009), and substance abuse disorders which persist during pregnancy often co-occur with affective or anxiety disorders. Alcohol and nicotine are estimated to be the most commonly used substances during pregnancy in the United States. For example, national survey self-report estimates of drug use during pregnancy indicate that 9–15% of women in the US consume alcohol, 17% smoke cigarettes, and 3.4% of women report any illicit drug use during pregnancy (Chang *et al*. 1998).

Substance abuse during pregnancy has significant adverse effects on the developing fetus. Consuming alcohol while pregnant increases the risk for first trimester spontaneous abortions, stillbirths, fetal growth restrictions, and typical fetal anomalies. Alcohol abuse during pregnancy is the most common preventable risk for child mental retardation (Chudley *et al*. 2005). Heavy fetal alcohol exposure in late pregnancy or during delivery can cause a neonatal withdrawal syndrome consisting of tremors, ventricular tachycardia, and seizures. Illicit drugs use during pregnancy poses risk of suboptimal pregnancy outcomes, and depending on the substance (e.g., amphetamines, opioids) can contribute to a higher likelihood of spontaneous abortions or premature deliveries, low birth weight, or neonatal withdrawal syndrome (see review Lester & Twomey, 2008).

Severe psychosocial stress

The presence of psychosocial stressors can trigger the onset of depression during pregnancy, or can exaggerate and maintain concurrent depression. Such stressors include exposure to trauma and violence, relationship conflict, and inadequate social support systems. The strain of poverty and resultant food, housing and financial insecurity may be further stressors.

Past physical or sexual abuse is common in women suffering substance use and mental health problems. In general, women in the US have a 68.9% chance of being exposed to noncombat related trauma including completed rape (12.65%), other sexual assault (14.32%), physical assault (10.28%), and childhood abuse (28%) (Resnick *et al*. 1993). Additionally, prior trauma and abuse experience increase the risk for revictimization (Widom *et al*. 2008) and women may be more likely to engage in abusive relationships.

Domestic violence during pregnancy poses a significant threat to a pregnant woman as well as the fetus (Parker *et al*. 1994). Exposure to violence and abuse can lead to adverse physical and mental health consequences for the affected women, including depressive and anxiety disorders. Screening for domestic violence and trauma is essential to begin to address the challenges faced by these affected women in an empathic and nonjudgmental way, and to create a supportive environment for change.

Pregnancy is a time of role transition for all women. The prospect of delivery and a new infant fundamentally alters a woman's role as a self-reliant individual, professional, and partner in various adult relationships, as well as the balance of power within the relationship. Screening for relationship satisfaction and the quality of the partner relationship are important as they allow providers to evaluate for relationship conflict, which may underpin the depressive illness and contribute to treatment resistance.

Stress related to lack of social support from the spouse, family and the larger community further confound depressive illnesses. In addition to such relationship stressors, housing and financial instability can aggravate depressive illness, confound treatment planning, and prevent full remission of antenatal depression. Case management and social work support to help women cope with these issues must be part of a comprehensive treatment package for depression during pregnancy.

Treatment options for depression during pregnancy

Psychiatric and/or psychosocial comorbidity, often coupled with women's reluctance to seek mental health services, pose challenges to effective treatment planning for depressed, pregnant women. These comorbidities and psychosocial stressors may interfere with rapid and positive treatment outcomes. To address these multiple and diverse challenges, a comprehensive, multidimensional approach is needed that addresses the biological, psychological, and social aspect of the illness. This requires the provision of treatment options on multiple levels including pharmacotherapy, psychotherapy, and social work/case management. Close monitoring of pharmacotherapy is paramount, given the complexity and changing nature of psychiatric symptoms. Engagement in interpersonal, cognitive and supportive therapy is essential,

so as to assist with role transition, to assert safety and support from a partner and to address symptoms of mental illness. Additionally, provision of social work support to assist with housing and income may help minimize psychosocial strain. In the next section, we will provide a brief overview of current state-of-the art treatment modalities for depression during pregnancy.

Pharmacotherapy

Antidepressants

There are few pharmacological standards for treatment of women with depressive disorders during pregnancy, in part because ethical constraints preclude randomized controlled trials using medication during gestation. In a recent publication (Yonkers *et al*. 2009), both the American Psychiatric Association and American College of Obstetrics and Gynecology suggested that women should consider the use of psychotherapy prior to considering medications, but that those with moderate to severe, recurrent depressive symptoms or suicidal thinking should remain on antidepressants during pregnancy. Many women are reluctant to seek treatment, but for those who do, some physicians are unsure of how to balance maternal medication requirements with risk of exposure to the growing fetus. Since many pregnancies are unplanned or undetected for some time, all women of childbearing age should have their depression managed as if pregnancy is possible. The primary care provider should engage in preconception planning with all women of childbearing age who are at risk of depressive illness. Decisions regarding the use of pharmacotherapy during conception and the first trimester are among the most critical for a woman and her physician. Women diagnosed with depression who have been asymptomatic for over a year may wish to attempt to reduce or discontinue antidepressants prior to conception and throughout the pregnancy (Gonsalves & Schuermeyer, 2006). Women should be closely monitored for relapse of symptoms. Women who discontinued their antidepressants during pregnancy experienced more relapsing symptoms (68%), compared with those who continued their medication regimen (26%) (Cohen *et al*. 2006). If a woman's depression history contains multiple relapses or severe symptoms such as suicide attempts and multiple inpatient psychiatric admissions, some recommend she remain on antidepressants for her own safety, regardless of pregnancy status (Gonsalves & Schuermeyer, 2006).

Although research studies indicate no major malformations are associated with antidepressant use during pregnancy, neither have they shown that any specific antidepressant is completely safe. All psychotropic medications cross the placenta and enter the amniotic fluid. General guidelines include some straightforward principles: (a) keep the medication regimen simple using monotherapy when possible; (b) discuss risks and consequences of both pharmacotherapy and untreated depression; and (c) choose agents with demonstrated fetal safety. Use of multiple medications in sequence as well as medication augmentation strategies all increases the exposure of the fetus (ACOG Practice Bulletin, 2008). The woman's history of prior response to pharmacotherapy should be considered when choosing a medication (ACOG Practice Bulletin, 2008). Although many factors influence pharmacotherapy during pregnancy, drugs with fewer metabolites, drug–drug interactions, more protein binding (preventing placental passage) and lesser teratogenic risk, if known, should be prioritized when possible (ACOG Practice Bulletin, 2008).

Spontaneous abortion. Research results are mixed when examining rates of antidepressant use and its relationship to spontaneous abortion, and may be confounded by the effect of the illness itself (Hemels *et al*. 2005). One study suggests that women taking antidepressants during pregnancy have a statistically significant higher rate of spontaneous abortion (3.9%) regardless of the type of antidepressant (Hemels *et al*. 2005), whereas, other studies show spontaneous abortion rates are elevated by exposure to several different antidepressant classes, but only exposure to bupropion is statistically significant (Chun-Fai-Chan *et al*. 2005; Einarson *et al*. 2009).

Teratogenicity. Research on antidepressant teratogenicity is growing and there is considerable scientific debate about the safety of antidepressants during pregnancy. Although the mainstream media has created controversy regarding the safety of SSRIs, the majority of research to date does not confirm major congenital malformations above the 2–4% baseline rate cited for the general population (Wichman *et al*. 2009). A recent meta-analysis confirmed no increased risk of major congenital malformations with in utero exposure to SSRIs (Einarson, 2009). In 2005, GlaxoSmithKline published a report based on a claims database study of 815 infants, which showed babies born to mothers who were taking paroxetine during their first trimester had a 1.5–2 fold increased risk of congenital heart defects, particularly atrial and ventricular septal defects (GlaxoSmithKline. 2005). A more recent study negated these findings demonstrating that the rate of cardiac defects for babies exposed to paroxetine in the first trimester and those babies not exposed was the same (0.7%), and within the expected cardiac malformation risk range for all pregnancies (Einarson *et al*.

Table 2. Use of antidepressants during pregnancy

Medication	Use during pregnancy/teratogenicity	Spontaneous abortion	Neonatal adaptation and monitoring at birth
SSRIs	No increased risk of teratogenicity above baseline rate (Einarson, 2009; Wichman *et al*. 2009) • Small risk of septal defects and other anomalies (GlaxoSmithKline. 2005) • Paroxetine controversial (GlaxoSmithKline. 2005; Alwan *et al*. 2007; Louik *et al*. 2007; Einarson *et al*. 2008)	Mixed findings (Chun-Fai-Chan *et al*. 2005) suggesting increased rates of spontaneous abortion regardless of type of antidepressant; findings may be confounded by impact of illness	30% of infants exposed have transient difficulty in first days of life (Koren *et al*. 2005) • Risk for pulmonary hypertension suggested in some (Chambers *et al*. 2006) but not all (Andrade *et al*. 2009) studies
TCAs	No increased risk of teratogenicity above baseline rate (Einarson, 2009)	Mixed findings (Chun-Fai-Chan *et al*. 2005) suggesting increased rates of spontaneous abortion regardless of type of antidepressant; findings may be confounded by impact of illness	Difficulties with neonatal adaptation, and withdrawal symptoms well established (Einarson, 2009)
SNRIs and other AD	No increased risk of teratogenicity above baseline rate (Einarson, 2009)	Buproprion exposure during pregnancy linked with significant risk for spontaneous abortion (Einarson *et al*. 2009)	Difficulties with neonatal adaptation, and withdrawal symptoms well established with venlafaxine

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitor; AD, antidepressant.

2008). At the time of this writing, the use of paroxetine continues to be debated among perinatal psychiatrists. Most practitioners choose other agents, except for those women who have demonstrated a past positive preferential response to paroxetine. When paroxetine is used, it is recommended that the fetus is monitored with fetal echocardiography (ACOG Practice Bulletin, 2008). While a 2007 study found no significant relationship between SSRIs and congenital cardiovascular malformations, the authors of that study suggest an association between SSRIs (especially paroxetine during the first trimester) and infants with anencephaly, craniosynostosis, and omphalocele (Alwan *et al*. 2007). These findings were refuted by another recent study finding no increased risk of these anomalies with SSRI use by pregnant women. They did, however, find some significant relationships between sertraline and omphalocele and between paroxetine and right ventricular outflow tract obstruction defects. Although these findings indicate some increased risk of specific rare birth defects with specific drug exposure, the overall absolute risk of birth defects with the use of SSRIs is small (Alwan *et al*. 2007; Louik *et al*. 2007).

Neonatal adaptation. Studies show that up to 30% of infants exposed to SSRIs in the third trimester are likely to have symptoms of poor neonatal adaptation (Koren *et al*. 2005). These symptoms include short-term self-limited cardiorespiratory symptoms, hypothermia, hypoglycemia, irritability, hyper and hypotonia, feeding disturbances, and seizures (Koren *et al*. 2005). These infants may have increased neonatal intensive care unit (NICU) admissions, in part due to vigilance of staff. Studies assessing neonatal outcomes and complications do not correct for commonly co-occurring risk factors (substance and tobacco use) (Ross *et al*. 2006). One author, correcting for these confounding variables, found no increased rate of premature labor or intensive care monitoring for babies exposed to SSRIs or venlafaxine in utero. As in other studies, some infants did exhibit neonatal adaptation syndrome symptoms (Ferreira *et al*. 2007). In a 2006 case-control study, infants exposed to SSRIs after 20 weeks gestation had a 1% increased risk of persistent pulmonary hypertension of the newborn (Chambers *et al*. 2006); however, another recent study refuted this increased risk (Andrade *et al*. 2009). While some international literature suggests tapering of SSRIs to avoid the late gestation exposure, most practitioners in the US avoid this, as it predisposes women to a substantially heightened risk of late pregnancy and postpartum morbidity secondary to depression (Einarson *et al*. 2001) and predisposes the infant to medication withdrawal symptoms in utero.

The bulk of the literature to date does not show increased risk of congenital malformations associated with pregnant women taking tricyclic antidepressants (TCAs) (Einarson, 2009). Doses of TCAs may need to be increased as much as 1.6 times the prepregnancy dose in the second half of pregnancy to establish therapeutic levels as a result of increased plasma volumes and metabolism (Sharma, 2006). Case reports have presented babies with TCA exposure as experiencing temporary withdrawal symptoms within the first 12 hours of life, including jitteriness, irritability, urinary retention, bowel obstruction, and occasionally seizures (Einarson, 2009). Nulman *et al*. found there

were no associations between a mother's use of TCAs or fluoxetine during pregnancy and the global IQ, language or behavioral development in preschool children (Nulman *et al*. 1997). Further research is needed to examine long-term outcomes for these children. Much more limited information is available regarding in utero exposure to atypical antidepressants such as bupropion, mirtazapine, nefazodone, trazodone, duloxetine, and venlafaxine; however, data so far indicate a satisfactory safety profile (Einarson, 2009). Like SSRIs and TCAs, venlafaxine has been implicated in cases of neonatal withdrawal (Einarson, 2009). See Table 2 for an overview of antidepressant use during pregnancy.

More recently, research suggests that exposure to medications may have adverse neonatal impact independent of maternal illness. For example, work by Oberlander and colleagues (2008) shows that length of prenatal SSRI exposure increases the risks of lower birth weight, neonatal respiratory distress and reduced gestational age even after controlling for maternal illness (Oberlander *et al*. 2008). Furthermore, this research group found that the association between prenatal SSRI exposure and adverse neonatal outcomes is moderated by a specific infant genotype in the serotonin transporter promoter region (SLC6A4; Oberlander *et al*. 2008). These findings suggest complex infant gene polymorphism by maternal prenatal medication interactions in explaining potential risk and vulnerability constellations for children exposed to maternal illness and/or prenatal medications.

Mood stabilizers

The challenges in managing women with bipolar disorder center around the potential risk of teratogenicity associated with the major mood stabilizers (Sharma, 2009).

Lithium had originally been associated with a substantially increased risk of Ebstein's anomaly, prompted in part by reporting of the 1970s International Register of Lithium Babies. Original estimates of Epstein's anomaly, reported at 400-fold higher than the general population, were called into question as a result of selective over-reporting of these anomalies within these retrospective registries. More recent pooled analyses of all scientific data estimated the risk of Ebstein's anomaly following first trimester lithium exposure to be 0.05–0.1%. This represents a relative risk 10–20-fold higher than the general population. Use of lithium in later pregnancy has, however, been associated with neonatal withdrawal symptoms in the infants. (Gentile, 2006).

Compared with lithium, the anticonvulsant medications may pose a somewhat greater risk of teratogenicity (Cohen, 2007). It is important to recognize, however, that the bulk of information about congenital anomalies with anticonvulsants comes from epilepsy literature, and it is well known that infants born to unmedicated epileptic women present an increased risk of major malformations, thus the relative risk of the anticonvulsants themselves is unknown (Holmes *et al*. 2001).

The overall rate of carbamazepine (CBZ) related teratogenicity is approximately 6%, with specific increases in rates of spina bifida ranging from 0.5–1% (Cohen, 2007). In addition, there have been sporadic case reports of coagulopathies, microcephaly, craniofacial anomalies, and growth retardation.

Valproic acid (VPA) or valproate may be an even more serious teratogen, conferring an approximately fivefold increased risk (11%) of major malformations when used within the first trimester. The relative risk of neural tube defects is 50-fold greater than the spontaneous rate, and occurs in 1–2% of all pregnancies exposed to valproate within the first trimester. Prenatal use of folate is essential in this population. Fetal exposure to valproate has been also associated with craniofacial anomalies and cognitive delays (Cohen, 2007).

Based on data from the Lamotrigine Prenancy Registry (2001), the estimated risk of congenital anomalies with lamotrigine monotherapy (2.5%) is similar to the base rate in the general population. Data from the UK Prospective Pregnancy Registry suggests a similar risk (Morrow *et al*. 2001). A recent paper from Europe refutes a previous report on increased risk of orofacial clefts (Dolk *et al*. 2008; Einarson, 2009).

Antipsychotics

Until recently, literature regarding the use of antipsychotics during pregnancy was limited to studies and case reports involving the conventional neuroleptics. High-potency typical neuroleptics such as perphenazine and haloperidol have shown relative safety in pregnancy (Einarson, 2009). For overview see Table 1. Studies of newer atypical antipsychotics are ongoing, but are insufficiently powered to definitely determine rates of teratogencity beyond the baseline rate; however, one recent study on pregnancy use of atypical antipsychotic medications did not show increased teratogenity (McKenna *et al*. 2005). The same study also reports increased rates of spontaneous abortions in the group using atypical antipsychotics compared to women not taking atypical antipsychotics (McKenna *et al*. 2005). See Table 3 for an overview of mood stabilizer use during pregnancy.

Benzodiazepines. Early studies reported increased risk of major malformation and oral cleft malformations,

Table 3. Use of mood stabilizers during pregnancy

Medication	Use during pregnancy/yeratogenicity	Neonatal adaptation	Monitoring at birth
Lithium	Increased risk of cardiovascular anomalies in the first trimester, but lower than initially stated (Gentile, 2006)	Neonatal withdrawal symptoms including respiratory symptoms, hypotonia, and poor neonatal adaptation (Gentile, 2006)	May be reinstituted in second trimester to prevent relapse of bipolar illness • Dosage should be increased in third trimester to control for increase plasma volume • Following delivery dosage should be decreased to prepregnancy levels • Fetal survey should be obtained at 18 weeks • Infants should be monitored following delivery for respiratory symptoms and tone (Cohen, 2007)
Valproic acid	First trimester use contraindicated; associated with high rates (up to 11%) of congenital anomalies, including neural tube defects (Holmes *et al*. 2001; Gentile, 2006; Cohen, 2007)	Poor neonatal adaptation reported in some infants, with cognitive delays seen longer term (Gentile, 2006)	When used in second and third trimester plasma levels should be monitored due to increased plasma volumes • Fetal survey essential at 18 weeks, and folate supplementation recommended • Compatible with breastfeeding (Cohen, 2007)
Lamotrigine	Limited data, but to date, relatively favorable • One study suggesting similar risk of major anomalies to population at large (Holmes *et al*. 2001)	Limited data	As in nonpregnant state; careful monitoring for rash • Monitor maternal LFTs
Antipsychotic agents	The high potency, first generation antipsychotics are best studied (haloperidol) with no clear evidence of increased risk of teratogencity (Einarson, 2009) • Case reports and small studies are emerging for the atypical agents, and while there is no clear evidence of teratogenic risk at this time, all studies are underpowered to be conclusive (Fisher *et al*. 1985; McKenna *et al*. 2005; Dolk *et al*. 2008)	No data	Continued monitoring for extrapyramidal side effects, CBC, LFTs, and EKG necessary in women using antipsychotics during pregnancy (Cohen, 2007)

CBC, complete blood count; LFTs, liver function tests; EKG, electrocardiography.

especially during first trimester exposure; however, recent studies do not confirm these previous reports (Einarson, 2009). High-dose use late in pregnancy may predispose the infant to neonatal withdrawal symptoms including hypotonia, neonatal apnea, or temperature instability (Fisher *et al*. 1985). While some authors conclude that third trimester discontinuation was indicated to avoid these sequelae, most conclude that such discontinuations would unnecessarily predispose women to a relapse of anxiety disorders.

ECT during pregnancy

ECT use during pregnancy is considered effective for treatment-resistant depression, relatively safe without risk of teratogenity, and has a moderate rate of adverse complications. Standard practice should include an obstetric consult to assess potential preexisting risk prior to the ECT procedure. For women in the second and third trimester of pregnancy, it is noteworthy that women should be positioned slightly toward their left side with support under the right hip when receiving ECT to prevent a vena caval compression syndrome (Rabheru, 2001).

Psychotherapy

Psychotherapy has been extensively studied in the treatment of depression and is empirically validated for treatment of mood disorders. Psychotherapy is recommended as the treatment of choice for mild–moderate depression (Yonkers *et al*. 2009), and should be included in the treatment of all women with treatment-resistant symptoms due to severity of illness and psychosocial issues seen in complicated treatment resistance (TRD). Interpersonal psychotherapy (IPT)

and/or cognitive behavioral therapy (CBT) are both evidence-based approaches for treatment of depression outside of pregnancy (Bhatia & Bhatia, 1999). There is very limited data, however, on CBT specifically timed during pregnancy. CBT has been investigated as modality for postpartum depressed women, and was found to be effective. IPT, which focuses on role transitions or role conflicts that may surface in the context of depression, may be particularly relevant for childbearing women since this may be a period of significant role transitions and role disputes with significant others. Studies have demonstrated effectiveness of IPT treatment during pregnancy and postpartum. See Misri and Kendrick for a review of CBT and IPT as treatment of depression during pregnancy (Misri & Kendrick, 2007).

Alternative treatments

There is limited, yet promising, data on bright light therapy during peripartum. Light therapy has been studied both during pregnancy and postpartum, and both applications are effective for reducing depressive symptoms (Misri & Kendrick, 2007).

Epidemiologic studies have demonstrated that consumption of two to three seafood meals per week is associated with decreased risk of depression and other mood disorders. ThejFish is the premier dietary source of the omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), neither of which are synthesized by the human body. During pregnancy and postpartum maternal omega-3 fatty acid stores are progressively depleted. Women in the US fall short of the recommended dietary intake, mainly because of fear of mercury-contaminated fish. However, omega -3 fatty acids are essential for healthy fetal brain development. While several studies to date have confirmed that intake of EPA and DHA is safe and beneficial as an adjunctive treatment for depression and bipolar depression (with effective doses ranging from 1–9 g per day across studies), only limited data is available during pregnancy and postpartum. Continued research on fish oil supplementation during peripartum is needed. Current guidelines recommend EPA and DHA supplementation to support mood stabilization of at least 1 g per day as capsules during or outside of childbearing, or at least two fish meals per week outside of pregnancy with concern regarding mercury contamination impacting guidelines for its consumption during pregnancy. For a meta-analysis of current studies, dosing recommendations, and safety considerations see the review by Freeman *et al*. (2006).

More recently, there has been interest in research on mind–body modalities, some of which have been practiced over thousands of years, such as progressive muscle relaxation, yoga, or awareness-enhancing meditation (Beddoe & Lee, 2008). While much of this research has methodological limitations (e.g., lack of randomized controlled trials) there seems to be converging evidence for the efficacy of mind–body modalities during pregnancy used in conjunction with prenatal care.

Conclusions and future directions

Treatment of depression during pregnancy is complex, almost always involving multimodal treatments and many providers including those in obstetrics, pediatrics, psychiatry, and child psychiatry. Coordination of care between such providers, and the relative merit of psychotherapeutic, supportive, and psychopharmacologic modalities all require further investigation. To date, the specific contribution of pharmacotherapy versus maternal illness and fetal risk is uncertain. Novel treatment strategies such as vagal nerve stimulation and transcranial magnetic stimulation are also untested during pregnancy. Numerous researchers are beginning to explore epigenetic influences on infants during gestation and the neonatal period. The impact of maternal illness on the infant's developing stress axis and predisposition to later psychiatric illness also merits further research. Moreover, how maternal depressive illnesses and treatment options impact upon infant capacity for self-regulation and temperament, subsequent attachment, cognitive development, and predisposition to psychiatric illness are all areas for further exploration.

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