New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum

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Maternal perinatal mental health has enormous consequences for the well-being of the mother, her baby, and the family. Over the last decade there has been a notable expanded awareness by health professionals and the general public of the importance of maternal perinatal mental health, and acknowledgement of the prevalence and morbidity associated with psychiatric illness during pregnancy and postpartum. Perinatal depression is defined as an episode of major depressive disorder (MDD) occurring either during pregnancy or within the first 6 months postpartum, and is one of the most common complications of the both the prenatal and postpartum period, with a prevalence of 10% to 15% in

Maternal perinatal mental health has enormous consequences for the well-being of the mother, her baby, and the family. Although it is well documented that perinatal depression is both common and morbid, with a prevalence of 10% to 15% in the general population, there remain many critically important unanswered questions about the pathogenesis of perinatal depression and most effective treatment regimens. Current lines of evidence from both human and animal models implicate hormonal dysregulation, abnormalities in hypothalamic-pituitary-adrenal axis activity, and the contributions of genetics and epigenetics as playing key roles in the development of perinatal reproductive mood disorders. Investigations into both human and animal models of perinatal depression offer much promise for the future identification of the underlying pathophysiology and subsequent early identification and/or prevention and appropriate treatment for women at risk for postpartum depression. Lastly, although it is generally accepted that pregnancy is not protective with regard to new onset or relapse of depression, the way to best treat maternal depression during pregnancy and lactation remains hotly debated. Future research in this area will more clearly elucidate the underlying pathogenesis, the potential long-term impact of perinatal depression on the developing fetus, and how best to counsel pregnant women about the risks of untreated major depressive disorder versus the risks of psychopharmacologic treatment during pregnancy and lactation.

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women of childbearing age.[1,2] Consistent documentation of the widespread prevalence of perinatal depression has led to recent recommendations for routine screening ("strongly encouraged but not mandated") for both antenatal and postpartum depression (PPD) by the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice in the US,[3,4] and the National Collaborating Center for Mental Health in the UK.[5] Australia and New Zealand have national recommendations stating that all perinatal providers have the responsibility to be aware of the risks for perinatal depression and to identify and refer for treatment as indicated.[6] In Norway, the government has endorsed an initiative to address mental health issues for women during pregnancy and after childbirth.[7] In the US, further evidence of support for perinatal depression was the 2010 passage of the Melanie Blocker Stokes MOTHERS Act, one component of the 2010 US Patient Protection and Affordable Care Act (PPACA). The MOTHERS act established a comprehensive federal commitment to combat postpartum depression through research, education, and voluntary support service programs.

However, although considerable progress has been made in terms of increasing public awareness, there remain many critically important unanswered questions and gaps in our understanding about perinatal depression. For example, there is still much to be learned about the underlying pathogenesis, the long-term impact of perinatal depression on the developing fetus, and how best to counsel pregnant women about the risks of untreated MDD versus the risks of psychopharmacologic treatment during pregnancy and lactation. This review will discuss these important issues and describe currently recommended treatment options based on the available literature.

Epidemiology of perinatal depression

Many good quality studies have documented that perinatal depression is both common and morbid.[1,2,8-10] Estimates of prevalence are about 12% in the general population, but higher in individuals from certain groups including those with a prior history of MDD and in those with a history of PPD.[2,10] In addition, an increased prevalence has also been noted in low-income women, which disproportionately affects ethnic minorities, particularly African-American and Hispanic women in the US.[11,12] Moreover, the perinatal period has been documented to be a time of high risk for psychiatric hospitalization, particularly in women with bipolar affective disorder and those with past histories of MDD.[13] Most importantly, the risk for maternal suicide is significantly elevated among depressed perinatal women, and maternal suicides account for up to 20% of all postpartum deaths, making it one of the leading causes of maternal mortality in the perinatal period.[14]

Perinatal depression can have devastating consequences for the affected woman, her children, and family,[15-18] and has been linked to poor childbirth outcomes such as preterm delivery and low birth weight[19,20] and to detrimental effects on maternal sensitivity in the postpartum period.[21,22] Mothers who are more sensitive and responsive to their children are more likely to have children with secure attachment, and therefore the symptoms of maternal depression can lead to unresponsive, inconsistent, unavailable, or rejecting care by the mother toward the child (ie, decreased sensitivity).[21,22] Consequently, depressed mothers are more likely to have infants with colic,[23] to be intrusive and harsh with their infants,[21,22] and to exhibit other impaired parenting behaviors such as lower rates of infant safety practices[17,18] such as car seats and childproof latches on cabinets,[24,25] and decreased healthy child development behaviors such as reading, singing, and playing games with their child.[26]

Moreover, children exposed to perinatal (either during pregnancy or postpartum) maternal depression have higher cortisol levels than infants of mothers who were not depressed[27-30] and this finding continues through adolescence.[30] Importantly, maternal treatment of depression during pregnancy appears to help normalize infant cortisol levels.[31] These findings may partially explain the mechanism for an increased vulnerability to psychopathology in children of mothers with perinatal depression.[32]

Perinatal depression can also significantly impact the relationship of the couple. Discord in the relationship between mother and partner has been identified as an important factor influencing both the development and outcome of PPD.[33,34]

Clinical presentation of perinatal depression

Mild mood and anxiety symptoms may be common during pregnancy and throughout the first days to weeks postpartum. In the early postpartum period,

mild mood symptoms lastly approximately 2 weeks or less are often called the "baby blues"; these symptoms usually resolve spontaneously with no sequelae. However, more severe and persistent mood and anxiety symptoms should arouse suspicion of PPD. The onset of PPD is usually within the first few months after childbirth, although some women report onset of symptoms during pregnancy. Distinguishing features of PPD may include severe anxiety, agitation, suicidal thoughts, and fears of hurting and/or lack of interest in the newborn.[2] Ruminating and obsessive thoughts during the perinatal period are increasingly documented as a presenting complaint among many women seeking treatment.[35,36]

Pathogenesis of perinatal depression

Although the pathogenesis of perinatal depression is currently unknown, it is an important area of ongoing research. Investigations into both human and animal models of perinatal depression offer much promise for the future identification of the underlying pathophysiology and subsequent early identification and/or prevention and treatment for women at risk for PPD. We will discuss current lines of evidence from both human and animal models that implicate hormonal dysregulation, abnormalities in hypothalamic-pituitary-adrenal (HPA) axis activity, and the contributions of genetics and epigenetics as playing key roles in the development of perinatal reproductive mood disorders.

Dysregulation of the HPA axis in reproductive endocrine mood disorders

The female reproductive steroid hormones, estrogen and progesterone, are derived from a common precursor, cholesterol. These hormones, in addition to their reproductive functions, have been shown to exhibit potent neuroregulatory effects on a range of nonreproductive behaviors including mood and cognition.[37] With the discovery of the estrogen receptor in 1962 by Jensen and Jacobson, a roadmap emerged for the cellular actions of steroid hormones.[37,38] Moreover, beginning with the work of Phoenix et al in 1959, there has been evidence to suggest that perinatal manipulation of reproductive steroids may have long-term consequences on brain sensitivity to these to steroids postpuberty.[37,39] These two pieces of animal model evidence laid the early framework which implicated hormonal dysregulation in vulnerable or susceptible women as part of the underlying pathogenesis of perinatal depression.

More recent work by Block et al demonstrates that, despite normal levels of reproductive hormones, women with PPD have an abnormal response to changes in reproductive steroid levels (estrogen and progesterone).[40] Additionally, there is increasing evidence that abnormalities in HPA axis activity play a key role in the etiology of both MDD as well as PPD.[41-45] Estrogen and progesterone have profound interactions with the HPA axis and may therefore trigger the HPA axis abnormalities in susceptible women.

Striking hormonal changes take place in the transition from pregnancy to the postpartum period.[46] The third trimester of pregnancy is characterized by high estrogen and progesterone levels and a hyperactive HPA axis (normal during pregnancy) with high plasma cortisol[47] which is stimulated in part by the high levels of estrogen and progesterone.[44] At the time of childbirth and during the transition to the postpartum period, estrogen and progesterone rapidly decline, and there is blunted HPA axis activity due to suppressed hypothalamic corticotrophin-releasing hormone (CRH) secretion.[43] The suppression may be due to the length of time it takes for the hypertropic adrenal cortexes (due to the hyperstimulated state during pregnancy), to progressively downsize and gradually return to normal.[43] As in nonpuerperal MDD, the HPA axis appears disturbed in women with PPD. Furthermore, although the trigger for PPD is likely heritable, the human and animal literature suggest that the onset of PPD is determined by the contributions of both genetics and life events.[48,49] Thus, it is important to briefly review the normal functioning of the HPA axis and how this differs in depressed (non-PPD) patients as compared with women with PPD.

In a *normal* HPA axis, the delivery of CRH from the paraventricular nucleus of the hypothalamus triggers the stimulation of adrenocorticotropic hormone (ACTH) from the anterior pituitary and, consequently, cortisol from the adrenal cortex. This hormonal system is regulated by negative feedback mediated by cortisol receptors in the anterior pituitary, hypothalamus, and hippocampus, as well as ACTH receptors in the anterior pituitary and CRH autoreceptors in the hypothalamus.[50] In *depressed patients*, it has been shown that there is a change in the regulation of the HPA axis.[51] A hallmark feature that characterizes the HPA axis in depression is

the altered response to stress and inability to maintain regulation: indeed, hyperactivity of the HPA axis is one of the most robust biological findings in major depression.[51]

Both women with PPD and women with nonpuerperal MDD show abnormalities in HPA axis activity. In general women (and men) suffering from MDD exhibit high baseline cortisol and an exaggerated response to the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test. However, in the first few weeks postpartum, euthymic women demonstrate an HPA axis that remains refractory to external CRH challenge. In contrast, women with PPD have been shown to experience an ongoing blunting of ACTH response to corticotrophin-releasing hormone (CRH) at 6 to 12 weeks postpartum compared with nondepressed women, interpreted as reflecting an ongoing hyporeactive HPA axis.[43] Additionally, Bloch et al observed that currently euthymic women with a past history of PPD experienced an increased cortisol response and onset of significant depressive symptoms when exposed to a protocol consisting of high-dose gonadal steroid administration followed by abrupt withdrawal. This observed effect in those women with a history of PPD was in marked contrast to the group of women without a history of PPD who experienced no observed mood disturbance when exposed to the same protocol. Thus, this work suggests either a trait vulnerability related to the onset of PPD or a consequence of an earlier depression.[45]

Interestingly, the HPA axis has also been a focus of recent efforts to identify a biomarker for those at risk for perinatal or postpartum depression. In particular, elevated placental CRH has been a potential candidate with earlier literature demonstrating conflicting results.[52,53] The increasing production of placental CRH (pCRH) throughout pregnancy can be measured in maternal peripheral blood[54] and within hours after childbirth, levels of pCRH quickly drop and become undetectable.[55] Nonetheless, the role of midpregnancy pCRH as a biomarker of maternal prenatal and PPD does not appear to be clinically useful, and the most recent report did not demonstrate an association between increased midpregnancy pCRH and increased risk for either depression during pregnancy nor PPD.[56]

Moreover, while the dysregulated HPA axis in PPD is interesting, disturbances in other endocrine systems may also play a role in the etiology of PPD. For example, one study has demonstrated that women with antenatal total and free thyroxine concentrations in the lower euthyroid range may be at greater risk of developing postpartum depressive symptoms.[57]

Animal models of genetic and epigenetic transmission of maternal anxiety and depression to offspring

In general, human studies of reproductive mood disorders are complicated by a variety of factors including lack of control over the subject's environment and genetic background, ethical issues of conducting research in pregnant and postpartum women, and inaccessibility of brain tissue required for analysis in certain studies. Therefore, animal models have been used successfully to model perinatal maternal behavior and to study the pathogenesis of perinatal anxiety, stress, and depression. The elegant and groundbreaking work in rodents by Meaney, Champagne, and colleagues[48,58] has demonstrated that maternal behavior during both pregnancy and postpartum has profound effects on both the physiological and psychological health of offspring. In particular, traumatic experiences in early life may be risk factors for the development of behavioral and emotional disorders that persist into adulthood. Franklin and colleagues recently reported that mice exposed to chronic and unpredictable maternal separation in the early postpartum period demonstrated depressive-like behaviors and alterations in their behavioral response to stressful environments when adults, particularly in males.[59]

Other recent animal literature demonstrates that maternal psychological status, in particular anxiety and depression during and immediately after pregnancy, confers increased vulnerability for mental illness in offspring. Furthermore, perinatal maternal depression and anxiety cause detrimental effects on maternal sensitivity, which may result in impaired mothering behaviors associated with insecure maternal/infant bonding and attachment.[48] Moreover, the consequences of impaired maternal-infant attachment occurring at a critical time for infant early brain development are serious and may lead to detrimental effects on both infant brain morphology and physiology, altered stress reactivity and socioemotional and neurocogitive development, as well as long-term behavioral and emotional problems persisting into adulthood.[48,58,60]

The emerging field of epigenetics, or the study of structural modification of chromosome regions leading to changes in gene expression caused by a mechanism other than changes in the DNA sequence, is a relatively new area of intense study.[61] Although these molecular changes involved in the epigenetics of the genome are complex, there is one particular mechanism that is thought to produce stable changes in gene expression. There are specific sites where a methyl group can attach to DNA via cytosine through an enzymatic reaction called methylation.[62] At a most basic functional level, methylation results in the silencing of the gene, and the bond formed between the DNA cytosine and the methyl group is strong, causing a stable but potentially reversible change in gene expression.[63] However, DNA methylation patterns can remain throughout the life of the cell and may be passed along for multiple generations potentially causing the organism's genes to behave differently, and providing an explanation for how early life experiences can leave an indelible mark on the brain and influence behavior and health in later life.[60] As an illustration of the above description, recent groundbreaking work in animal models of behavioral epigenetics have documented changes in the methylation status of individual genes in response to mothering behavior.[58,60,64] For example, the observation that adult behaviors in the rat could be influenced by the quality of maternal care early in life[65] suggested an epigenetic mechanism. Franklin and colleagues demonstrated in rats that the stress of chronic and unpredictable early life maternal separation in offspring altered the profile of DNA methylation in the promoter of several candidate genes in the germline of the separated males.[59] Additionally, Weaver, Champagne, and colleagues discovered that poor maternal care directly increased methylation in the promoter region of the glucocorticoid receptor gene, effectively reducing the number of receptors and resulting in heightened response to stress.[60] Methylation of the estrogen receptor (ER) alpha gene has also been documented in rats who, as a product of poor nurturing, go on to display poor maternal behavior.[66] Specifically, Champagne et al demonstrated increased methylation in response to maternal care in the promoter region of the estrogen receptor (ER) alpha gene which is implicated in induction of the oxytocin gene.[66] The oxytocin gene codes for the oxytocin hormone which promotes mother-infant attachment and affects maternal behavior.

Therefore, although behavioral epigenetics is a new area of study that offers an opportunity to define the nature of gene-environment interactions during development, there is much that remains unknown and future research is needed in order to disentangle the genetic, environmental, and epigenetic mechanisms that mediate maternal behavior and subsequent infant outcomes.

Controversies in the treatment of depression during pregnancy and postpartum

Although it has become generally accepted knowledge that pregnancy is not protective with regard to new onset or relapse of MDD,[67,68] how best to treat depression during pregnancy and lactation remains hotly debated. Nonetheless, despite the ongoing controversies surrounding treatment, psychotropic use during pregnancy has become relatively common with a two- to fourfold increase in use over the past decade despite a stable prevalence of psychiatric illness.[69,70] Moreover, recent reports have documented that up to 13% of all pregnant women are using an antidepressant during pregnancy.[70] In particular, the selective serotonin reuptake inhibitors (SSRIs) are the first-line, most frequently used antidepressants among pregnant women[70,71] The choice of whether to prescribe a medication during pregnancy is a difficult one, and prescribing must take into account the potential risks and benefits to the unborn infant and the mother. To date, the literature on the safety of antidepressants during pregnancy has yielded conflicting results that can be difficult to apply toward practical clinical recommendations. As elegantly stated by Rubinow in his 2006 *American Journal of Psychiatry* editorial on antidepressant treatment of pregnant women, "our therapeutic confusion derives in part from the requirement to calculate risk profiles for two individuals (mother and infant), involving multiple predictors and outcomes."[72] Unfortunately, calculation of risk based on high-quality studies is challenging because research focused on women during pregnancy or postpartum (and during lactation) present substantial ethical and practical challenges for the investigator, thus compromising the rapid accumulation of reliable data.[73] However, despite the absence of a large evidence base to guide treatment recommendations, the clinician must carefully discuss treatment options with the woman suffering from perinatal depression so that an understanding of the risk:benefit ratio of treatment versus no treat-

ment is achieved. Accordingly, the decision to use antidepressant medication during pregnancy or lactation must be weighed against the risks of untreated maternal depression and this risk:benefit ratio must be carefully discussed and tailored to the individual needs with each patient. A recent and helpful development in the creation of evidence-based practice guidelines for perinatal depression was the 2009 publication by Yonkers et al: a joint report on the management of depression during pregnancy endorsed by the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) and published simultaneously in both *General Hospital Psychiatry* and *Obstetrics and Gyencology*.[74,75] This report represents the first time that the APA and ACOG have collaborated to create practice guidelines for clinicians, and as such, signifies a significant contribution to the field. The report states that both MDD and antidepressant exposure are associated with fetal growth changes and shorter gestations, and that the current literature was unable to control for the possible effects of a depressive disorder in women and their infants exposed to an antidepressant during pregnancy (thus complicating interpretation of the risks associated with antidepressant use during pregnancy).[75]

Weighing risks and benefits of antidepressants during pregnancy

There are significant risks associated with exposure to untreated depression during pregnancy that are associated with serious adverse consequences for the developing neonate, such as premature birth, low birth weight, and future behavioral disturbances.[76,77] Studies have shown that terminating antidepressant treatment in pregnancy in women with a previous history of depression leads to relapse of symptoms in as many as 60% to 70% of women.[67,68] Relapse then exposes the developing infant to the effects of untreated depression, which has potentially devastating consequences for the patient, infant, and family. Untreated depression during pregnancy is also one of the strongest risk factors for the development of PPD. However, maternal antidepressant use during pregnancy has been associated with documented risks to exposed infants including persistent pulmonary hypertension of the newborn (PPHN) and a neonatal withdrawal/toxicity syndrome.

Persistent pulmonary hypertension

PPHN is a failure of the pulmonary vasculature to decrease resistance at birth. This results in significant breathing difficulties for the infant, hypoxia, and usually leads to intubation. PPHN has about a 10% to 20% mortality rate, and also results in significant morbidity.[78] It is a very rare condition, affecting 1 or 2 infants out of 1000 in the general population,[79,80] and has been associated with a number of factors including maternal smoking,[81] maternal diabetes, sepsis, meconium aspiration, and C-section, among others.[80]

Studies on the association between SSRIs and PPHN have yielded conflicting results, although more recent studies suggest the risk for PPHN following SSRI use during pregnancy is far less than originally estimated. The first report was published by Chambers et al in 2006 and is the basis for the FDA alert issued in July 2006 regarding the possible association of PPHN with SSRI antidepressants.[82] A second study was conducted through the Swedish Medical Birth Register for the years 1997 to 2005 and examined 831 324 women who had given birth during this time.[83] Antidepressant use was identified at the first antenatal care visit (usually first trimester) and through prescriptions written by the antenatal health service. Of 506 infants with PPHN, 11 had been exposed early in pregnancy to an SSRI which generated a relative risk estimate of 2.01 (CI 1.00-3.60). When only those cases that had a known exposure late in pregnancy and were born at or after 37 weeks were included the relative risk rose to 3.70 (CI 1.01-9.48).[83] More recently, a study from the HMO Research Network Center for Education and Research on Therapeutics found no differences between groups in prevalence of PPHN between infants exposed versus those not exposed to SSRIs during the third trimester.[71] One issue that complicates interpretation of these studies is that several factors that are associated with the development of PPHN in the general population, including maternal smoking, maternal diabetes, and high prepregnancy BMI are also associated with MDD and psychiatric disorders in general. It is also important to keep the potential elevated risk in perspective by considering the absolute risk. If one assumes that SSRIs increase the odds of the development of PPHN 6 times the rate in the general population, only 6 to 12 (0.6% to 1.2%) infants exposed to SSRIs will develop PPHN out of 1000 exposed. Thus, approximately 99% of women who take SSRIs during pregnancy will give birth

to a healthy infant who does not develop PPHN. In contrast, the risks associated with untreated depression during pregnancy are much higher and more frequent.[72]

Withdrawal/toxicity symptoms

The first report of withdrawal symptoms in babies exposed to antidepressants occurred in 1973.[84] It is unclear if "neonatal withdrawal syndrome" is actually a result of withdrawal from the antidepressant medication or is due to a toxicity mechanism. Thus, an alternative term such as "poor neonatal adaptation," or "neonatal neurobehavioral syndrome" may be a better description. Although there are a number of limitations in the available literature in this area, including inconsistent definitions, regardless, the FDA instituted a class labeling change in 2004 for both SSRI and SNRI (serotonin-norepinephrine reuptake inhibitors) antidepressants warning that third trimester exposure to antidepressants may be associated with signs and symptoms consistent with the syndrome. According to the label change, "reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying." The subsequent result has been that many practitioners have recommended tapering antidepressants prior to labor and delivery even though most cases of the neonatal syndrome appear to be very mild, self-limited, and do not appear to be associated with lasting repercussions[85] Recently, investigators in British Columbia studied whether adverse neonatal outcomes were reduced by stopping SSRI use before the end of pregnancy in a large cohort study that linked maternal health and prenatal SSRI prescription claims data to more than 119 000 neonatal birth records.[86] After controlling for possible confounding factors, including severity of maternal illness, the results showed neonatal outcomes did not improve when SSRI medications were stopped before the last 2 weeks of gestation and provided evidence that some adverse neonatal outcomes may not be consequent to an acute pharmacological condition such as toxicity or withdrawal.[86] Oberlander and Gingrich have reported on animal model literature describing neurobehavioral consequences of prenatal SSRI exposure.[87] This preclinical work shows that in animal models, early changes in serotonergic tone have molecular, neuroanatomical,and functional consequences, which are dependent on the timing (critical periods) and direction (increased or decreased) of change.[87] Clearly, larger, prospective human studies of the syndrome as well as strategies to minimize the incidence rate of the syndrome are needed. However, to date, there is no evidence from a safety perspective to recommend tapering of antidepressants in the third trimester, particularly in cases of moderate to severe maternal mental illness. Keeping the mother psychiatrically well should be the overarching goal of treatment during pregnancy for both the mother and the baby. In addition, the literature clearly documents that untreated depression in pregnancy carries a 6-fold increased risk for postpartum depression.[88]

Specific antidepressants and pregnancy

In general, many practitioners will prescribe SSRI medications during pregnancy since they are well-tolerated. Overall, with one exception (paroxetine), there does not appear to be an increased risk of major malformations with exposure to antidepressants in utero, though for many agents there is little to no data available.[75,89,90] More recently, some studies have not confirmed the earlier reports of increased risks of cardiac septal defects associated with paroxetine and some studies have found very weak associations with septal defects for both sertraline and citalopram.[91] However, overall, of the SSRI medications, both fluoxetine[92,93] and sertraline[93,94] have more data regarding safety than the newer SSRIs such as escitalopram and the SNRIs.[75,89,93,94] As first trimester exposure to paroxetine has been associated with cardiac defects in some studies, but not all, it should not be used as a first-line agent, but may be considered if the patient has responded well in the past.[4,74] The older tricyclic antidepressants should also be considered for use during pregnancy if they have been efficacious for the patient in the past, though side effects, particularly constipation and orthostatic hypotension, may be exacerbated by pregnancy.[75] There is limited data on the use of SNRIs, bupropion, mitazapine, and monoamine oxidase inhibitors, although reported risks appear to be small and these agents may be appropriate in a particular patient if they have been efficacious in the past.[74]

Antidepressant use in the postpartum period and during lactation

In the postpartum period,the literature demonstrates that women with PPD are likely to respond to standard

antidepressant therapy, and one class of antidepressant medication has not been proven to be superior to another.[95] The risks of exposure to antidepressant therapy in the postpartum period are primarily focused on the exposure of the infant to the antidepressant in breast milk.[95] Most of the literature examining the safety of lactation with antidepressant use has found low rates of adverse events in infants exposed to antidepressants, including tricyclics and SSRIs.[95] In particular, most studies show few adverse events and low or undetectable plasma levels with sertraline, paroxetine, and fluvoxamine.[96] Sertraline, in particular, appears to have the lowest concentration of transmission into breast milk and should be strongly considered as first line use for lactation.[93,95] The long half-life of fluoxetine and the potentially high breast milk concentrations of citalopram make these SSRIs less desirable choices.[96] Overall, the degree of infant exposure to medication in breast milk is affected by the rate of absorption into maternal circulation, diffusion from maternal circulation to breast milk, and absorption of the agent by the infant. Therefore, as a general recommendation, taking medication immediately after breast-feeding minimizes the amount present in milk and maximizes clearance before the next feeding.[97]

Regarding lactation, in the United States, all major medical organizations recommend exclusive breastfeeding for the first 6 months of life including The American Academy of Pediatrics[98] and The American College of Obstetrics and Gynecology.[99] Consequently, although 75% of mothers initiate breastfeeding, only 12 continue to breastfeed exclusively through 6 months.[100,101] Much of this early weaning is involuntary: in a recent study, more than half of mothers reported that they stopped breastfeeding earlier than they had desired.[102] Curtailed breastfeeding is associated with maternal depression, and neuroendocrine pathways underlying both lactation and regulation of maternal mood may play a central role.

Psychotherapy during pregnancy and postpartum

There are multiple psychotherapeutic techniques, including individual cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT), as well as group therapy that may be helpful in patients with mild-to-moderate depression.[75,103,104] IPT for pregnant and postpartum women has been shown to ameliorate depression during pregnancy and postpartum.[104-107] In addition, partner-and family-assisted therapies have shown efficacy for the treatment of perinatal depression.[108] Some women with mild-to-moderate symptoms of depression may prefer a psychotherapeutic treatment option to the risks of medication exposure. For women with more severe symptoms of depression, a combination treatment approach consisting of psychotherapy and medication may be the best option.

Practical guidelines and clinical recommendations

A collaborative and multidisciplinary treatment approach with the psychiatrist, obstetrician, and pediatrician is critical in order to educate the patient about both the risks of untreated depression and potential side effects to mother and baby associated with psychotropic exposure during pregnancy and/or lactation. Some practical guidelines (*Table I*) for counseling the patient in order to ensure optimal outcomes include the following: (i) A past psychiatric history should always be obtained as it will influence the selection of the treatment modality. The psychiatric history should include any prior episodes of depression, a history of hypomanic or manic episodes, severity of those episodes, potential triggers of mania including past antidepressant exposure, timing (prior PPD), as well as treatment history and documentation of prior response to antidepressant medication; (ii) Minimize the number of exposures for the baby. It is important to minimize the number of psychotropic medications used but also consider exposure to psychiatric illness an exposure. Changing the medications used dur-

- A multidisciplinary team approach is best to maximize outcomes
- Obtain a careful and thorough past psychiatric history
- All medication changes should be done prior to pregnancy if possible
- Limit the number of exposures for the baby; consider active depression in the mother an exposure
- Prescribe medications with the best documented evidence base
- Consider whether the mother plans to breastfeed when planning treatment
- If a baby was exposed to a medication during pregnancy, it may not make sense to discontinue the medication (or alternatively not breastfeed)
- Discuss psychotherapy as a treatment option

Table I. Practical guidelines for treating depression during pregnancy and postpartum.

ing pregnancy into the postpartum period when breastfeeding increases the number of exposures. For example, it is common for a woman on a newer antidepressant to become pregnant and then to receive the recommendation to switch antidepressants to an older medication that has more evidence for safety during pregnancy. While this might have made sense prior to pregnancy, this plan would actually increase the exposures for the baby. First, the baby has already been exposed to the newer antidepressant, and switching to a second medication would be another exposure. In addition, the likelihood that the patient could relapse while switching is high, thus exposure to the mood disorder would be a third exposure for the child; (iii) Consider whether the mother plans to breastfeed and discuss whether the medication can be safely used during breastfeeding and what the plan would be for monitoring the medication during breastfeeding; (iv) Discuss psychotherapy treatment options.

Conclusions

Perinatal depression is often debilitating to the woman experiencing it and to her family. Screening must be a routine part of postpartum care as there are effective treatments available that can prevent needless suffering. Although the etiology of perinatal depression remains unclear, headway is being made toward a better understanding of the complicated interplay of reproductive steroids (estrogen and progesterone) with the HPA axis and other neuroregulatory systems implicated in depressive illness. Further study of the alterations in the HPA axis during the transition from pregnancy to the postpartum period may provide new insights into the pathophysiology of perinatal mood disturbances. Animal studies have been used successfully to model perinatal maternal behavior and to study the pathogenesis of perinatal anxiety, stress, and depression. In addition, the rapidly growing field of behavioral epigenetics offers an intriguing area of study that may provide new insights into the nature of gene-environment interactions during development. Future research will help to disentangle the complex genetic, environmental, and epigenetic mechanisms that mediate maternal mental illness during the perinatal period including the subsequent influence on maternal behavior and infant outcomes.

Regarding treatment of depression during pregnancy, antidepressant use in pregnant women is often necessary in order to prevent maternal psychiatric illness. Recent collaborative consensus statements by the American Psychiatric Association and the American College of Obstetricians and Gynecologists provide a useful framework for the interpretation of data about the safety of psychotropic medications during pregnancy and lactation. Therefore, individualized recommendations based on the patient's past history should ideally be implemented prior to pregnancy with a goal of minimizing exposures.

In the postpartum period, commonly prescribed antidepressant medications used to treat PPD appear to be well tolerated by both nursing mothers and their infants and rates of adverse events are low. However, the baby will be exposed to the antidepressant in breast milk, and therefore, the patient and her partner should discuss both the risks versus benefits of lactation with their obstetrician and pediatrician.

Finally, it is critical that more research is conducted in the area of perinatal psychiatry in order to address the gaps in the literature, including: (i) prospective studies that further our understanding of the safety of antidepressant exposure in pregnancy and during lactation; (ii) longitudinal neurodevelopmental studies of children exposed to maternal mental illness, with or without psychotropics during pregnancy; and (iii) translational research that elucidates the underlying the pathophysiology of perinatal reproductive mood disorders with the long-term goal of ensuring the best possible clinical outcomes for mother and child. ❑

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Nuevas reflexiones sobre la depresión perinatal: patogénesis y terapéutica durante el embarazo y el postparto

La salud mental materna perinatal tiene enormes consecuencias para el bienestar de la madre, su bebé y la familia. Aunque está bien documentado que la depresión perinatal es frecuente y mórbida, con una prevalencia del 10% a 15% en la población general, aun persisten muchas preguntas de gran importancia acerca de la patogénesis de la depresión perinatal y los esquemas terapéuticos más efectivos que no han sido respondidas. Las actuales líneas de evidencia de los modelos humanos y animales revelan alteraciones en la regulación hormonal, en la actividad del eje hipotálamo-hipófisis-adrenal y en la genética y la epigenética, factores que juegan un papel clave en el desarrollo de los trastornos afectivos reproductivos perinatales. Las investigaciones en modelos humanos y animales de depresión perinatal ofrecen muchas promesas para la futura identificación de la fisiopatología subyacente y la consecuente identificación y/o prevención precoz y el tratamiento apropiado para las mujeres con riesgo de depresión postparto. Por último, aunque en general está aceptado que el embarazo no es protector en relación con la aparición o recaída de la depresión, la mejor manera de tratar la depresión materna durante el embarazo y la lactancia se mantiene en pleno debate. A futuro la investigación en esta área clarificará mejor la patogénesis subyacente, el potencial impacto a largo plazo de la depresión perinatal en el desarrollo del feto y cómo aconsejar mejor a la mujer embarazada acerca de los riesgos de un trastorno depresivo mayor no tratado versus el riesgo del tratamiento psicofarmacológico durante el embarazo y la lactancia.

Nouveaux regards sur la dépression périnatale : pathogenèse et traitement durant la grossesse et le postpartum

La santé mentale maternelle périnatale a des conséquences considérables sur le bien-être de la mère, de son bébé et de la famille. Alors que la dépression périnatale est connue pour sa fréquence et sa morbidité, avec une prévalence de 10 % à 15 % dans la population générale, sa pathogenèse et les traitements les plus efficaces dans sa prise en charge font l'objet de nombreuses questions essentielles restant sans réponse. Un certain nombre de données actuelles issues de modèles humains et animaux, impliquent les troubles hormonaux, les anomalies de l'activité de l'axe hypothalamo-hypophyso-surrénalien, la génétique et l'épigénétique dans le développement des troubles de l'humeur périnatals. La recherche sur des modèles humains et animaux de dépression périnatale est très prometteuse pour l'identification future de la physiopathologie sous-jacente et l'identification précoce et/ou la prévention et le traitement approprié des femmes à risque de dépression du postpartum. Enfin, bien qu'il soit généralement accepté que la grossesse ne protège pas contre la survenue ou la rechute d'une dépression, la meilleure façon de traiter la dépression maternelle pendant la grossesse et l'allaitement fait toujours débat. La recherche à venir dans ce domaine devrait permettre d'élucider clairement la pathogenèse sous-jacente, l'impact potentiel à long terme de la dépression périnatale sur le développement du fœtus et la façon de conseiller au mieux les femmes enceintes sur la balance bénéfice/risque des troubles dépressifs majeurs non traités en regard d'un traitement psychopharmacologique pendant la grossesse et l'allaitement.

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