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Recent Advances and Controversies in Peripartum Depression

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Abstract

Purpose of Review—The purpose of this review is to update readers on recent controversies and findings on the underlying biology and clinical management of peripartum depression.

Recent Findings—Topics discussed include the discovery and replication of two epigenetic biomarkers of peripartum depression, two well controlled studies that do NOT find associations between in utero antidepressant exposure and cardiac defects and persistent pulmonary hypertension of the newborn and ongoing controversy on whether antidepressant use during pregnancy prevents peripartum depression and whether or not hormonal treatments have a place in the management of postpartum depression.

Summary—Peripartum depression, or depression during and/or immediately following pregnancy is a unique psychiatric illness that not only may have unique biological underpinnings but demands unique and thoughtful approaches to management due to the developing neonate. A number of controversies exist in this area ranging from the recent terminology change in psychiatry's Diagnostic and Statistical Manual from “postpartum” to “peripartum” depression, to the safety of antidepressant use during pregnancy, to whether or not antidepressants prevent or decrease peripartum depression. Research in this area is growing and a number of exciting developments have occurred including the identification of two epigenetic biomarkers of peripartum depression that may eventually lead to early identification and intervention, the potential for hormonal treatments and the recommendation for and early institution of universal screening for peripartum depression. These topics are explored and put into context from a clinical management perspective.

Keywords

Peripartum Depression; Pregnancy; Postpartum; Epigenetic Biomarkers; Estrogen; Antidepressants

Conflict of Interest

Jennifer L. Payne declares grant support from the NIH and Sage Therapeutics, as well as personal fees from Astra Zeneca, Eli Lilly, Johnson and Johnson, and Pfizer for legal consulting. She also declares a patent issued for DNA Methylation Biomarkers of Postpartum Depression Risk.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Summarizing the burgeoning literature on the topic of Peripartum Depression over the last few years is no easy feat. The field of reproductive psychiatry as a whole is rapidly growing as evidenced by the growing number of conferences dedicated to women's mental health and the growing number of clinical and research fellowships focused on this topic. The U.S. Preventative Services Task Force recently recommended universal screening for depression in pregnant and postpartum women (1) and several states have already moved towards universal screening during pregnancy and after delivery and are emphasizing education and treatment in this vulnerable population (2). There are many exciting topics and findings in Peripartum Depression over the past several years. We have tried to address a number of timely and important topics here but fully admit that due to space constraints we have surely missed others. We will focus on topics of clinical significance particularly to obstetricians and gynecologists.

DSM-5: Postpartum versus Peripartum

The Diagnostic and Statistical Manual (DSM) (3) defines and delineates precise definitions and required symptoms for psychiatric disorders. The DSM recently published its 5th edition (DSM-5) which updated and changed the previous version (DSM-IV) in a number of areas. As part of the updated mood disorders section, the DSM-5 replaced DSM-IV's "postpartum" specifier with the more general term "peripartum." According to DSM-IV, the postpartum specifier should be used when a mood episode (depressive, manic or mixed) begins in the immediate (4 weeks) postpartum time period. In contrast, the "peripartum" specifier for DSM-5 can be used when a mood episode begins either during pregnancy OR within 4 weeks of delivery. In describing the change, the DSM-5 committee noted that 1) up to 50% of all major depressive episodes identified postpartum actually began during pregnancy, 2) they could identify no clear epidemiological evidence that postpartum depressive episodes were different from depressive episodes that began at other times in one's life, and 3) the specifier mechanism is meant to be used to identify subgroups of patients that need special care or treatment, which applies to pregnant women as well as women in the postpartum time period.

There are a number of advantages to the change. The term "peripartum" recognizes that depression (and other mood disorders) occur during pregnancy which is important since there has been an incorrect tradition of believing that pregnancy is protective against mood disorders. The change also recognizes that treatment of mood disorders during and immediately after pregnancy is complicated and risky and deserves special attention. The change is also likely to improve social acceptance of the need for treatment of mood disorders during and after pregnancy. However, from a research perspective, there is a loss of important data by lumping together depression and other mood episodes that begin during pregnancy with mood episodes that begin immediately afterwards. There are a number of lines of scientific evidence that support the idea that depressive episodes that begin in the immediate postpartum time period may be biologically distinct from depressive episodes that occur at other times of life, including epidemiological (4), hormonal sensitivity (5) and genetic vulnerabilities (6–10) the details of which are beyond the scope of this review,

though we review an example of this literature below (epigenetic biomarkers). For the practicing clinician, the change from “postpartum” to “peripartum” may primarily serve as a reminder that pregnant women do develop psychiatric illnesses that need treatment. Clinicians should keep in mind, however, that as research advances it may become important from a clinical perspective to determine whether or not a depressive episode began during or after pregnancy as the timing of onset may ultimately have treatment implications (see hormonal treatments below).

Universal Screening

The U.S. Preventative Services Task Force recently recommended universal screening for depression in pregnant and postpartum women (1) based on their finding that “programs combining depression screening with adequate support systems in place improve clinical outcomes (i.e. reduction or remission of depression symptoms in adults, including pregnant and postpartum women” (11). Universal screening for pregnant and postpartum women has already been attempted in several states. For example, in 2006, New Jersey became the first state to require postpartum depression screening (12) but it soon became apparent that it was important to have “adequate support systems in place.” Data from New Jersey’s Medicaid program demonstrated good rates of screening but low rates of transition to care (12). There was no change in the trend of treatment initiation in the six months following delivery from before the initiation of the law. This brings to light one of the primary issues facing psychiatry today: identification of psychiatric illness often does not translate into appropriate psychiatric follow-up care. There are a number of reasons for this including stigma and limited numbers of psychiatric providers leading to long wait-times and lack of referral sources. These issues point to a need not only for growing the number of psychiatric treatment providers, but also for providing basic education and knowledge to more front-line providers including family practice physicians, internal medicine doctors, obstetricians and pediatricians so that more physicians are able to prescribe and manage basic psychiatric problems. Massachusetts has focused on this approach by developing the Massachusetts Child Psychiatry Access Project (MCPAP) for Mom’s program which focuses on providing trainings, toolkits and telephone access to perinatal consultations for providers (13) New Jersey’s disappointing outcome also highlights the need for easily available referral sources. For example, a recent publication (14) examined the rates of screening and treatment in a large cohort (n=97,678) of pregnant patients at Kaiser Permanente in California prior to, during and after implementation of the Universal Perinatal Depression Screening Program conducted in Kaiser obstetrics clinics. In contrast to the study conducted in New Jersey, this study found a significant increase in the number of women screened as well as an increase in the number of women who received treatment for severe depression symptoms. The authors note that a strength of the program was “the collaboration with mental health care specialists” indicating the readily available referral sources within the Kaiser system contributed to the improved treatment outcomes.

Infant Outcomes with Prenatal Exposure to Antidepressants

One particularly controversial area, especially for obstetricians as well as psychiatrists, is whether or not the use of antidepressants during pregnancy is safe for the exposed neonate.

The literature on this topic is not only large but conflicting and one truly needs to examine the literature as a whole in order to interpret it and come to conclusions about the safety of antidepressant exposure during pregnancy. One significant limitation of the literature on this topic is that the use of psychotropic medications during pregnancy is essentially a “marker” for a population of women with different risk factors than the general population of pregnant women. These risk factors may influence the outcomes of studies attempting to examine the risks of in utero exposure to a psychotropic medication to a child. For example, diabetes, obesity, smoking, and substance use are more common in patients with psychiatric illness than in the general population. Studies which have not controlled for the underlying psychiatric illness and its attendant risks may find associations between psychotropic medications and outcomes that are not caused by exposure to the medication itself, but by the presence of other risk factors that are highly prevalent in the population of patients who take psychotropic medications during pregnancy. Two elegant studies conducted by the same group (15, 16) and published over the past two years nicely illustrate this point.

Some but not all previous studies demonstrated a possible association between in utero antidepressant (particularly Selective Serotonin Reuptake Inhibitors (SSRI)) exposure and heart defects (reviewed in (17)). However, most of these studies were “confounded by indication” meaning they compared psychiatric population outcomes to the general population instead of psychiatric population outcomes in patients with Major Depression who took antidepressants during pregnancy to women with Major Depression who did not take antidepressants during pregnancy thus effectively controlling for the underlying illness as well as its attendant risk factors and behaviors. For example, Hubrecht’s et al. (15), the largest study to date, with a sample size of over 900,000 women, did not find an association between first trimester antidepressant exposure and cardiac malformations when the analyses controlled for the underlying illness, Major Depression. Because of the large sample size, the authors were able to compare the outcomes of women with depression who took antidepressants to outcomes of women with depression who did not take antidepressants in the first trimester, thus controlling for the illness itself. This finding supports other studies which have attempted to control for Major Depression and its associated behaviors and risk factors which did not find an association between in utero antidepressant exposure and cardiac defects. For example: Wang et al. (18) performed a meta-analysis of prospective cohort studies and found no association between SSRI use in the first trimester and heart defects when comparing women with depression who took SSRIs in the first trimester with women with depression who did not take antidepressants in pregnancy. Thus, the previously identified association between in utero antidepressant exposure and heart defects appears to most likely be associated with other risk factors and behaviors that are prevalent in the population of women taking antidepressants in pregnancy and not due to exposure to the antidepressant itself.

A similar story has evolved for the association between in utero antidepressant exposure and persistent pulmonary hypertension (PPHN) in the newborn. An association between SSRI exposure and PPHN was first noted in 2006 by Chambers et al (19) and was the basis for the FDA Alert issued that year regarding the possible association of SSRIs and PPHN. Since this first study, six additional studies have been conducted: three found no association between SSRI exposure and PPHN (20–22) and two found an association (23, 24) although

with lower odds ratios than the first. The sixth and most recent, once again performed by Huybrecht's et al (16) analyzed nearly 3.8 million pregnancies, including 128,950 women who took an antidepressant during pregnancy, and found an odds ratio of 1.51 (CI 1.35–1.69) for an association between SSRI exposure and PPHN in the unadjusted analysis. However, when the analyses were adjusted for potential confounders associated with Major Depression, the odds ratio became insignificant (odds ratio 1.10 [0.94–1.29]).

Another example of the complexities of determining whether in utero antidepressant exposure is safe is provided by a recent study that examined the effects of untreated depression on neonatal outcomes (25). This meta-analysis examined neonatal outcomes in women with depression receiving no treatment and compared them to outcomes in women without depression. This study found that untreated depression was associated with significantly increased risks of preterm birth and low birth weight indicating that exposure to the illness Major Depression in utero affects infant outcomes. This finding complicates interpretation of previous studies that found associations between antidepressant exposure and low birth weight and preterm birth as taking an antidepressant during pregnancy does not guarantee that a woman was not depressed AND taking an antidepressant. These studies demonstrate the complexities of sorting out what exposure is associated with neonatal outcomes when the use of a particular medication during pregnancy is not the only potential exposure associated with the use of the medication.

Do Antidepressants Prevent Peripartum Depression?

Another area of controversy is whether or not antidepressants, when used during pregnancy, prevent the development of peripartum depressive episodes. The available literature is conflicting as to whether or not antidepressant use during pregnancy decreases the development of a depressive episode either during or after pregnancy. Cohen et al (26, 27) found in an observational study that the discontinuation of medication during pregnancy results in a high relapse rate during pregnancy. This study was conducted in a high-risk population. In contrast, in another observational study Yonkers et al (28) found in a community sample that the risk for onset of a depressive episode either during or after pregnancy was essentially the same whether or not antidepressants were continued or discontinued. Our own data demonstrate that psychiatric medication treatment may not protect some women from peripartum depression though the lack of medication use increased the risk for depression. We followed 93 pregnant women during and after pregnancy with a history of a mood disorder in order to determine outcomes and identify clinical characteristics that precede the development of peripartum depressive episodes (8). All women were managed by their treating psychiatrist as clinically indicated. We found that 75.4% of the sample met DSM-IV criteria for a major depressive episode either during pregnancy, postpartum or both. We modeled depression in a given time period (second trimester, third trimester, or one month postpartum) as a function of medication use during the preceding period (first, second or third trimester) and found that the odds of being depressed for those who did not use medication in the previous period was approximately 2.8 times that of those who used medication (OR 2.79, 95% CI, $p = .0048$). Thus, the lack of medication increased the subsequent risk of depression. At the same time, medication use was not necessarily protective: 39.4% of women who were well prior to delivery went on to

develop a postpartum depressive episode, despite the fact that 80% were taking psychiatric medications. Thus the use of psychiatric medications during pregnancy may not protect against depression in women at high risk. These conflicting results likely reflect population differences and it is probable that there are particular factors, such as a personal or family history of peripartum depression, that increase the risk of peripartum depression regardless of medication use. Another factor that is likely to play a role is that many women may attempt to take lower doses of medication during pregnancy or may be reluctant to increase medication during pregnancy despite evidence that serum levels of psychiatric medications decrease over the course of pregnancy (17). The developing infant then is exposed not only to the medication, but also to the effects of the depression itself.

Epigenetic Biomarkers for Peripartum Depression

A series of studies aimed at identifying biomarkers of peripartum depression, have demonstrated that two genes, HP1BP3 and TTC9B, exhibit different patterns of methylation for peripartum depression that develops during pregnancy and continues versus pure postpartum depression that develops shortly after delivery. The genes were originally identified as genetic loci that were responsive to high dose estrogen in the mouse hippocampus; these loci were then cross-referenced with DNA methylation differences in samples of blood from women with pre-existing mood disorders who were clinically well during pregnancy and either did or did not develop postpartum depression. Two loci were identified at the HP1BP3 and the TTC9B genes, which were able to correctly identify whether a woman did or did not develop postpartum depression with an accuracy of greater than 80%. However, in a replication sample of women who became depressed during pregnancy and either did or did not continue to be depressed postpartum, the two loci, particularly HP1BP3 loci, were methylated in the opposite direction. For example in the sample of women who were well during pregnancy, those who developed postpartum depression demonstrated increased methylation at HP1BP3 while in the sample of women who were depressed during pregnancy, those who remained depressed postpartum demonstrated decreased methylation at the HP1BP3 gene. Incorporation of blood count data as a proxy for inflammation accounted for the discrepancy and allowed for prediction of postpartum depression or continued depression postpartum depression with an accuracy of greater than 80% for the entire sample. Blood count data was incorporated based on the observation that women who were depressed during pregnancy had higher WBC's and elevated granulocytes indicative of depression-associated inflammation in comparison to women who were psychiatrically well during pregnancy. Because the identified biomarkers demonstrated methylation changes in the opposite direction dependent on whether or not the subject was depressed during pregnancy versus postpartum, it was important to separate the two groups or the biomarkers would not have been identified. Importantly, these findings have recently been replicated in two samples: one in an independent sample of 51 pregnant women with pre-existing mood disorders as well as a sample of 240 pregnant women without a previous psychiatric diagnosis (29). These findings are important as they may point to a future test for postpartum depression that can be taken during pregnancy. While it remains to be seen what interventions can be undertaken to prevent the onset of postpartum depression or continuation of a depressive episode into the postpartum time period the

ability to identify women at high risk will be invaluable in the future. These findings also support the continued use of the “postpartum” specifier as opposed to the more inclusive “peripartum” specifier in psychiatric research.

Estrogen for Postpartum Depression

Postpartum depression occurs within four weeks following parturition according to both DSM-IV and DSM-5 criteria and follows a dramatic drop in the circulating levels of estradiol and progesterone. While depression risk is not predicted by serum levels of gonadal hormones in humans (5, 30), rapid withdrawal from these hormones may be a key factor in triggering postpartum depression. Bloch et al. (5) were the first to demonstrate that women with a history of postpartum depression display mood sensitivity to hormonal changes: They administered supra-physiological doses of estrogen and progesterone to simulate the levels found in pregnancy to a group of women with and without a history of postpartum depression. Upon blinded withdrawal from this hormone-mediated pseudo-pregnancy, only the women with a postpartum depression history experienced significantly depressed mood symptoms (5, 30). Two early trials suggested that estradiol (E2) treatment may alleviate postpartum depression. Gregoire et al. (31) randomized 61 women who developed depression within 3 months of delivery to placebo or an E2 patch and found that 80% of the E2-treated women responded compared to 31% of the placebo group. An open-label trial of sublingual 17 β -estradiol (1mg 3–8 times daily depending on serum estradiol) was undertaken in 23 women in-patients with symptoms of severe postpartum depression (32). After 2 weeks of treatment 19 of the 23 achieved remission of their symptoms. However, nearly half of the estrogen-treated patients were also receiving antidepressants making it difficult to determine if the estrogen or the antidepressant improved depressive symptoms. Despite these tantalizing results, over a decade passed without further testing of E2 in the treatment or prevention of postpartum depression. Wisner et al. (33) published a long-awaited pilot randomized trial using transdermal E2, sertraline or placebo. Unfortunately the study was stopped after it was found that serum E2 concentrations were lower than expected and that transdermal E2 doses greater than 100 μ g/d did not increase serum concentrations. Of note, the mean serum E2 concentration was nonsignificantly higher in those who responded compared to those who did not respond (93.6 pg/ml, SD 65.8 for responders versus 56.1 pg/ml, SD 56.5 for nonresponders, $p=0.24$). These surprising results leave open the question of whether or not E2 treatment for postpartum depression is a viable option. The authors speculated that obesity, induction of cytochrome P450 E2 elimination pathways in pregnancy and possibly suppression of endogenous E2 secretion in the setting of exogenous E2 may have played a role. Future research in this area is likely.

Conclusions

The clinical management of mood disorders, particularly depression, during and after pregnancy is a controversial area with a lot of questions, few answers and little research to guide treatment decisions. The studies presented in this paper demonstrate that, while much more research needs to be done, we are starting to at least glimpse the complexities involved in making treatment recommendations during this critical time period. For example, a large literature exists examining infant outcomes with in utero exposure to antidepressants-

however, the most recent studies have become increasingly sophisticated and use better methods of controlling for confounding factors that may influence outcomes. Currently, these studies are more reassuring than earlier studies that did not control for confounds and also indicate that exposure to depression the illness is an exposure that influences outcomes for the child. The literature also demonstrates conflicting data on whether or not antidepressant use during pregnancy decreases the risk of peripartum depression-however, close examination of the literature points out that the question is not so simple as do antidepressants prevent peripartum depression but whether or not there should be antidepressant management strategies during pregnancy to improve outcomes since pregnancy presents a unique set of variables, including weight gain and metabolic changes that may influence outcomes. This question was also highlighted by the recent study addressing the use of E2 in postpartum depression. Future research will need to concentrate on clinical management strategies that ideally prevent peripartum depression rather than treat it once it has developed. To that end, the studies identifying epigenetic biomarkers of peripartum depression will be useful in identifying women at high risk for these illnesses and will allow for research on prevention. With the U.S. Preventative Services Task Force's recommendation to institute universal screening for perinatal depression, research in this area will need to expand so that we can provide evidence-based treatments for the many women that will be identified and seek care. Ideally, in the future screening with questionnaires, interviews and blood tests will be able to identify women at risk and there will be answers and guidance on how to psychiatrically manage these women during and after pregnancy. Prevention of peripartum depression is hopefully in our future.

References

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

• Of importance

•• Of major importance

- **1. O'Connor, E.; Rossom, RC.; Henninger, M.; Groom, HC.; Burda, BU.; Henderson, JT., et al. Screening for Depression in Adults: An Updated Systematic Evidence Review for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. This review provides support for the recommendation to screen all pregnant and postpartum women for depression
2. Farr SL, Denk CE, Dahms EW, Dietz PM. Evaluating universal education and screening for postpartum depression using population-based data. *J Womens Health (Larchmt)*. 2014; 23(8):657–63. [PubMed: 25072299]
3. APA. Diagnostic and statistical manual of mental disorders. Washington DC:
4. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Archives of general psychiatry*. 2008; 65(7): 805–15. [PubMed: 18606953]
- *5. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *The American journal of psychiatry*. 2000; 157(6):924–30. This classic study provides the first evidence of mood sensitivity to hormonal fluctuation in women with postpartum depression. [PubMed: 10831472]

6. Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Goes FS, Schweizer B, et al. Genome-wide linkage and follow-up association study of postpartum mood symptoms. *The American journal of psychiatry*. 2009; 166(11):1229–37. [PubMed: 19755578]
7. Payne JL, MacKinnon DF, Mondimore FM, McInnis MG, Schweizer B, Zamoiski RB, et al. Familial aggregation of postpartum mood symptoms in bipolar disorder pedigrees. *Bipolar Disord*. 2008; 10(1):38–44. [PubMed: 18199240]
8. Kimmel M, Hess E, Roy PS, Palmer JT, Meltzer-Brody S, Meuchel JM, et al. Family history, not lack of medication use, is associated with the development of postpartum depression in a high-risk sample. *Archives of women's mental health*. 2015; 18(1):113–21.
9. Forty L, Jones L, Macgregor S, Caesar S, Cooper C, Hough A, et al. Familiality of postpartum depression in unipolar disorder: results of a family study. *The American journal of psychiatry*. 2006; 163(9):1549–53. [PubMed: 16946179]
10. Murphy-Eberenz K, Zandi PP, March D, Crowe RR, Scheftner WA, Alexander M, et al. Is perinatal depression familial? *Journal of affective disorders*. 2006; 90(1):49–55. [PubMed: 16337009]
11. Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016; 315(4):380–7. [PubMed: 26813211]
12. Kozhimannil KB, Adams AS, Soumerai SB, Busch AB, Huskamp HA. New Jersey's efforts to improve postpartum depression care did not change treatment patterns for women on medicaid. *Health Aff (Millwood)*. 2011; 30(2):293–301. [PubMed: 21289351]
13. Byatt N, Biebel K, Moore Simas TA, Sarvet B, Ravech M, Allison J, et al. Improving perinatal depression care: the Massachusetts Child Psychiatry Access Project for Moms. *Gen Hosp Psychiatry*. 2016; 40:12–7. [PubMed: 27079616]
14. Avalos LA, Raine-Bennett T, Chen H, Adams AS, Flanagan T. Improved Perinatal Depression Screening, Treatment, and Outcomes With a Universal Obstetric Program. *Obstet Gynecol*. 2016; 127(5):917–25. [PubMed: 27054938]
15. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *The New England journal of medicine*. 2014; 370(25):2397–407. [PubMed: 24941178]
16. Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Paterno E, Gopalakrishnan C, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *Jama*. 2015; 313(21):2142–51. [PubMed: 26034955]
17. Chisolm MS, Payne JL. Management of psychotropic drugs during pregnancy. *Bmj*. 2016; 532:h5918. [PubMed: 26791406]
18. Wang S, Yang L, Wang L, Gao L, Xu B, Xiong Y. Selective Serotonin Reuptake Inhibitors (SSRIs) and the Risk of Congenital Heart Defects: A Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association*. 2015; 4(5)
19. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *The New England journal of medicine*. 2006; 354(6):579–87. [PubMed: 16467545]
20. Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiology and drug safety*. 2009; 18(3):246–52. [PubMed: 19148882]
21. Wichman CL, Moore KM, Lang TR, St Sauver JL, Heise RH Jr, Watson WJ. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. *Mayo Clinic proceedings*. 2009; 84(1):23–7. [PubMed: 19121250]
22. Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *American journal of perinatology*. 2011; 28(1):19–24. [PubMed: 20607643]
23. Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. *Pharmacoepidemiology and drug safety*. 2008; 17(8): 801–6. [PubMed: 18314924]

24. Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *Bmj*. 2012; 344:d8012. [PubMed: 22240235]
- *25. Jarde A, Morais M, Kingston D, Giallo R, MacQueen GM, Giglia L, et al. Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2016 This study compares outcomes for infants among pregnant women with depression who are taking antidepressants and pregnant women with depression who are not taking antidepressants. This is one of the first studies to attempt to examine the effect of depression on pregnancy outcomes for infants in the absence of antidepressant use.
26. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006; 295(5):499–507. [PubMed: 16449615]
27. Cohen LS, Nonacs RM, Bailey JW, Viguera AC, Reminick AM, Altshuler LL, et al. Relapse of depression during pregnancy following antidepressant discontinuation: a preliminary prospective study. *Archives of women's mental health*. 2004; 7(4):217–21.
28. Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL, et al. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology*. 2011; 22(6):848–54. [PubMed: 21900825]
29. Osborne L, Clive M, Kimmel M, Gispén F, Guintivano J, Brown T, et al. Replication of Epigenetic Postpartum Depression Biomarkers and Variation with Hormone Levels. *Neuropsychopharmacology*. 2015
30. Bloch M, Rubinow DR, Schmidt PJ, Lotsikas A, Chrousos GP, Cizza G. Cortisol response to ovine corticotropin-releasing hormone in a model of pregnancy and parturition in euthymic women with and without a history of postpartum depression. *J Clin Endocrinol Metab*. 2005; 90(2):695–9. [PubMed: 15546899]
31. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet*. 1996; 347(9006):930–3. [PubMed: 8598756]
32. Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. *The Journal of clinical psychiatry*. 2001; 62(5):332–6. [PubMed: 11411813]
33. Wisner KL, Sit DK, Moses-Kolko EL, Driscoll KE, Prairie BA, Stika CS, et al. Transdermal Estradiol Treatment for Postpartum Depression: A Pilot, Randomized Trial. *J Clin Psychopharmacol*. 2015; 35(4):389–95. [PubMed: 26061609]