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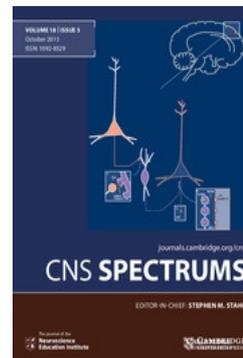
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# The management of mood disorders in pregnancy: alternatives to antidepressants

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The management of mood disorders during pregnancy is complex due to risks associated with medication use and risks associated with untreated depression. Antidepressant use during pregnancy is an exposure for the unborn child, and it currently remains unclear what long-term repercussions there might be from this exposure, though available data are reassuring. On the other hand, there are risks for both the mother and child of untreated depression during pregnancy. There is a real need for research into nonpharmacological strategies for the prevention of relapse of mood disorders in pregnant women who are off medications. We have reviewed a number of potential candidate interventions including psychotherapies, exercise, light box therapy (LBT), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), holistic strategies, and nutritional and herbal supplements. Currently there is a lack of evidence supporting the use of such strategies in the prevention of depressive relapse during pregnancy, though most of these strategies have at least some support for their use in the treatment of a major depressive episode. Carefully conducted research using one or more of these strategies in women who want to discontinue antidepressants for pregnancy is sorely needed.

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**Key words:** Peripartum, depression, mood disorder, persistent pulmonary hypertension, holistic, poor neonatal adaptation.

## Clinical Implications

- There are risks to the developing child from the use of antidepressants during pregnancy and, in turn, risks to both mother and child of untreated depression during pregnancy.
- The discontinuation of antidepressants for pregnancy is associated with a high relapse rate of depression.
- Nonpharmacological interventions that prevent or prophylax against relapse of mood disorders during pregnancy are needed.
- Though more research needs to be done, potential alternative interventions that could be used to treat or potentially prevent relapse of depression during pregnancy include psychotherapy, exercise, light box therapy (LBT), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), alternative “holistic” interventions, and nutritional and herbal supplements.

## Introduction

The choice of whether to prescribe a medication during pregnancy is a difficult one that must take into account

the potential risks and benefits of both treatment and nontreatment to the unborn infant and the mother. When the mother is diagnosed with a potentially life threatening illness, the choice of whether to prescribe a medication often becomes obvious. However, when the mother faces an illness that is not viewed as immediately life threatening, such as a mood disorder, the decision to prescribe becomes more complicated. One such area of controversy is the use of antidepressants during pregnancy.<sup>1</sup> Perinatal depression has an estimated prevalence rate of at least 10%<sup>2–5</sup> in the general population, and this rate approaches 25% or higher<sup>6</sup> in women with a history of major depressive disorder (MDD) or bipolar disorder. Rates of antidepressant medication during pregnancy and lactation have continued to rise in North America over the past decade,<sup>1,7,8</sup> and antidepressant use during pregnancy is now estimated to be at least 7%<sup>8–10</sup> of all pregnancies.

The choice of whether to use an antidepressant medication during pregnancy often generates strong opinions and confusion, leaving women with mood disorders and their physicians unsure of how to proceed. There are several issues that complicate the interpretation of what little data exist. For example, there are two people involved, including both the mother and the developing child, and at times they have competing interests. There are also few studies that have attempted to separate out the effects of exposure to depression from the effects of exposure to

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medication. Most studies are complicated by the frequent use of multiple medications and the lack of long-term follow-up studies. In addition, though there are documented risks of exposure to psychiatric medications, such as antidepressants, in utero, the majority of exposed infants do not develop an associated adverse outcome, and it remains unclear what influences these differences. For example, particular environmental exposures or genetic risk factors could, in theory, influence outcomes in infants exposed to medications in utero. Finally, some of the controversy surrounding the use of psychiatric medications during pregnancy is a direct result of the continued lack of understanding of the risks associated with untreated psychiatric illness and the common belief that antidepressants and other psychiatric medications are “luxury” medications that should be stopped in the setting of pregnancy. Women with mood disorders who want to have a child are therefore “stuck between a rock and a hard place”: If they stop their medications for pregnancy, they run the risk of relapse and exposing their developing child to depression, and if they do not stop their medications, they expose their developing child to the medication. There is a clear need for interventions that would allow women to discontinue their antidepressant medications for pregnancy but prevent relapse of their mood disorder. Techniques that prolong time to relapse or even prophylax against relapse altogether would help ensure that many women would be able to discontinue their medications for pregnancy and still remain well. The goals of this review are to discuss the current literature summarizing the risks associated with the use of antidepressants during pregnancy, to review the current literature summarizing the risks associated with untreated depression during pregnancy, and to discuss potential alternatives to antidepressant use during pregnancy.

### **The Risks Associated with Antidepressant Use During Pregnancy**

A complete and thorough discussion of the literature investigating the risks associated with the use of antidepressants during pregnancy is beyond the scope of this review. The interested reader should review the 2010 report issued by the American Psychiatric Association and the American College of Obstetricians and Gynecologists.<sup>11</sup> The available literature is at times conflicting and is complicated by the frequent use of multiple medications, the difficulty of controlling for maternal psychiatric illness and comorbid health behaviors (such as smoking, lack of exercise), and the difficulty of controlling for length of exposure and dosage. We have briefly reviewed the primary conclusions of the available literature below:

#### *The impact of antidepressant use on birth outcomes*

A number of studies have demonstrated a slightly increased risk for miscarriage with the use of antidepressants early in pregnancy. In a meta-analysis, this risk has been estimated at 12.4% in women who took antidepressants versus 8.7% for women who did not.<sup>12</sup> Antidepressant use has also been associated with reductions in birth weight and preterm birth.<sup>11</sup>

#### *The impact of antidepressant use on major organ malformations*

The available literature has not consistently identified specific organ malformations associated with the use of antidepressants during pregnancy. Paroxetine use during the first trimester has been associated with a higher risk of cardiac malformations by some studies<sup>13–15</sup> but not others.<sup>16,17</sup> One study found that the combination of a benzodiazepine with a SSRI, but not a SSRI alone, increased the incidence of congenital heart defects. The overall consensus in the field is that the risk of major organ malformations, if it exists, is small in the setting of antidepressant monotherapy.<sup>11</sup>

#### *Antidepressant use and persistent pulmonary hypertension*

Persistent pulmonary hypertension (PPH) is a failure of the pulmonary vascular resistance to decrease at birth and, if severe, is fatal. Known risk factors for PPH include obesity, maternal smoking, diabetes, C-section, meconium aspiration, and sepsis, among others. There have been 6 studies to date examining the association between selective serotonin reuptake inhibitor (SSRI) antidepressant use late in pregnancy and PPH: 3 have been positive<sup>18–20</sup> and 3 have been negative.<sup>21–23</sup> Complicating the interpretation of these studies is the fact that several known risk factors are more common in the psychiatric population, and not all of these factors were controlled for in all studies. The risk of PPH is extremely rare, thus the absolute risk to exposed babies is very low, with greater than 99% of exposed infants *not* developing this syndrome.

#### *The use of SSRIs during the third trimester and poor neonatal adaptation (PNA)*

A constellation of symptoms that has been collectively termed poor neonatal adaptation (PNA) has been detected in approximately 30% of infants exposed to SSRIs during the third trimester.<sup>24,25</sup> PNA is defined loosely as a cluster of symptoms including tachypnea, hypoglycemia, temperature instability, irritability, a weak or absent cry, and seizures.<sup>11,26</sup> This syndrome has also been identified in infants exposed to tricyclic antidepressants<sup>27</sup> and other centrally acting classes of

medications including anti-epileptic drugs and anti-histamines,<sup>28</sup> and is therefore not specific to SSRIs. Symptoms are usually transient, and the underlying mechanism is unclear. PNA has been regarded as reflecting a toxicity reaction and/or a withdrawal syndrome, among others.<sup>11</sup> Whether or not the presence of PNA portends more persistent effects on infant or child developmental outcomes is currently unknown.

### **The Risks Associated with a Major Depressive Episode (MDE) During Pregnancy**

#### *Discontinuation of antidepressants for pregnancy is associated with a high relapse rate of MDD*

Terminating antidepressant treatment in pregnant women with a history of MDD has been shown to lead to relapse in 60–70% of women.<sup>29,30</sup> Relapse then exposes the developing infant to the effects of untreated depression, which leads to adverse consequences for the patient, infant, and family.<sup>11,31,32</sup> Women with MDD are therefore left with a difficult choice of whether to expose their babies to the risks of untreated depression or to the risks of antidepressant use during pregnancy.

#### *Exposure to a MDE in utero is associated with poor outcomes for the exposed infant*

There is evidence that exposure to a MDE in utero is associated with poor outcomes for the infant as well.<sup>11</sup> It remains unclear whether these undesirable outcomes are associated with the underlying biological consequences of the MDE itself (such as elevated cortisol levels) or whether they are a result of behavioral changes in the mother when she is depressed. Antenatal depression has been associated with low maternal weight gain<sup>11</sup>; increased rates of preterm birth<sup>11,33</sup>; low birth weight<sup>11</sup>; increased rates of cigarette, alcohol, and other substance use<sup>34</sup>; increased ambivalence about the pregnancy; and overall worse health status.<sup>35</sup> Children exposed to perinatal (either during pregnancy or postpartum) maternal depression also have higher cortisol levels than infants of mothers who were not depressed,<sup>36–39</sup> and this continues through adolescence.<sup>39</sup> Importantly, maternal treatment of depression during pregnancy appears to help normalize infant cortisol levels.<sup>40</sup> While the long-term effects of elevated cortisol levels remain unclear, these findings may partially explain the mechanism for an increased vulnerability to psychiatric conditions in children of mothers with antenatal depression.<sup>41</sup> In summary, exposure to maternal depression in utero should be considered an exposure for the developing infant that, just as with an exposure to a medication, may result in undesired outcomes and risks.

### **Untreated depression during pregnancy is associated with postpartum depression**

Untreated depression during pregnancy is one of the strongest risk factors for the development of postpartum depression (PPD). PPD has potentially devastating consequences, including suicide and infanticide. While the risk for suicide deaths and attempts is lower during and after pregnancy than in the general population of women, suicides account for up to 20% of all postpartum deaths and represent one of the leading causes of peripartum mortality.<sup>42</sup> PPD has been associated with significantly increased rates of infantile colic and impaired maternal–infant bonding.<sup>43</sup> PPD also interferes with parenting behavior, including less adequate infant safety and healthy child development practices,<sup>44</sup> such as the increased use of harsh discipline.<sup>45</sup> Likely due to changes in parenting behavior, exposure to postpartum depression is also associated with slower language development, more behavioral problems, and lower IQ in the child.<sup>46</sup> Depression either during or after pregnancy is therefore a risk exposure for the child, and given the high relapse rate of depression during pregnancy when antidepressants are stopped (up to 70%), the lack of antidepressant use during pregnancy in a woman with a mood disorder cannot be considered a more benign intervention.

### **Clinical Management of Women with Mood Disorders During Pregnancy**

Only 20–30% of pregnant women report that antidepressants are an acceptable treatment option for depression during pregnancy.<sup>47</sup> In this study, the majority of pregnant women stated that if depressed, they would opt for either talk therapy or no treatment at all.<sup>47</sup> Ideally, conversations about treatment should begin prior to pregnancy onset, and both the patient and her clinician should have a good understanding and plan of what the preferred treatment should be and what would happen if the patient relapsed with her mood disorder while pregnant.

For women who are clinically well prior to attempting pregnancy, the decision of whether or not to continue antidepressants during pregnancy is a difficult one. On one hand, continued antidepressant use exposes their child to the medication. On the other, discontinuation has a good chance of exposing the child to the illness itself, which, as discussed, is a significant risk factor for poor outcomes. Interventions that could be used to prevent relapse of depression after discontinuation of antidepressants during pregnancy would represent a large step forward in the management of mood disorders during pregnancy. Unfortunately there are few studies that have specifically

looked at interventions that prevent relapse during pregnancy; however there are a number of alternative interventions that could potentially be used in this manner, though data on prevention of relapse are generally lacking. These include psychotherapy, exercise, light box therapy (LBT), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), alternative or “holistic” interventions and nutritional and herbal supplements (Table 1). We briefly review each below:

### *Psychotherapy*

There are many studies of various types of psychotherapy, including group psychotherapy, and other psychosocial interventions for the treatment of antenatal and/or postpartum depression. Reviews of these studies have generally concluded that well-designed randomized trials are needed in order to determine if any of these therapies is effective in this particular population.<sup>48–50</sup> The most rigorously studied intervention is interpersonal therapy (IPT). O'Hara *et al.*<sup>51</sup> reported a randomized (but not blinded) study of IPT versus wait list control in 120 postpartum women who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria for a MDE and found improved outcomes in the IPT intervention. One version of IPT, partner assisted IPT, was specifically developed for perinatal depression and demonstrated promising results in a preliminary proof of concept trial in women who were depressed either during or after pregnancy.<sup>52</sup> A number of studies have examined the efficacy of cognitive behavior therapy (CBT), but overall have not used strong designs.<sup>50</sup> Other work has also provided support for the use of supportive or nondirective counseling.<sup>50</sup> In terms of prevention of depression in groups of women at high risk for perinatal depression, again the most promising appears to be IPT.<sup>53</sup> The literature in this area is limited, however, as it is mixed with various definitions of “at risk” status, small sample sizes, fewer treatments than usual (for example with CBT), and the use of clinicians who are not experts in the intervention under study.<sup>50</sup> One promising prevention strategy that has not been studied in the population is the use of mindfulness-based cognitive therapy, which has been shown to significantly reduce rates of depressive relapse in adults with recurrent major depression.<sup>50,54,55</sup> Further work in this area is needed.

### *Exercise*

Exercise has been shown to reduce the risk for MDD. Population-based studies strongly support the role of regular physical activity as an intervention that protects against the onset of MDD.<sup>56</sup> For example, Blumenthal *et al.*<sup>57</sup> studied 156 adults with MDD who

were randomly assigned to aerobic exercise, sertraline, or both, and found that exercise was equally as effective as antidepressant medication in reducing depressive symptoms. An extension of this study found that the exercise group had significantly lower relapse rates than subjects in the medication group.<sup>58</sup> The same group went on to complete a placebo-controlled trial of 202 adults diagnosed with MDD and assigned to one of the following conditions: (1) group exercise, (2) home exercise, (3) medication, or (4) placebo.<sup>59</sup> Although there was a high placebo response, the exercise groups improved as much as the medication group, indicating that efficacy of exercise might be equivalent to medication in the treatment of MDD.<sup>59</sup> Finally, a recent study found that aerobic exercise during pregnancy reduced depressive symptoms in women with no psychiatric history.<sup>60</sup> This suggests that exercise may decrease the risk of relapse of depression in women with MDD who want to stop their antidepressants for pregnancy. Once again, more work needs to be done to test this hypothesis. Commitment to exercise is difficult for many people, and doing so while pregnant may be even more difficult. However, for the motivated patient who wants to stay off medication while pregnant, exercise may represent a viable alternative.

### *Light box therapy*

LBT has been established as an appropriate therapy for seasonal affective disorder (SAD), in which a person experiences repeated bouts of major depression usually during the fall and winter when there is less daylight.<sup>61,62</sup> The observation that exposure to light alters circadian rhythms and suppresses melatonin secretion is thought to be the biological basis of its positive effects.<sup>63,64</sup> Light therapy in general is well-tolerated and safe, and therefore has a very favorable risk-to-benefit ratio<sup>65,66</sup> as well as ophthalmologic safety.<sup>67</sup> A number of studies have demonstrated the efficacy of LBT in nonseasonal MDD (for example, Kripke *et al.*,<sup>68</sup> Kripke,<sup>69</sup> and Yamada *et al.*<sup>70</sup>). One meta-analysis found that there was a significant reduction in depression severity with LBT with an effect size equivalent to those in antidepressant trials.<sup>71</sup> A systematic review of LBT in nonseasonal depression found that most studies in this area poorly controlled the issue of placebo and were limited by small sample sizes.<sup>72</sup> Despite these limitations, the reviewers concluded that, “Overall, bright light therapy is an excellent candidate for inclusion into the therapeutic inventory available for the treatment of nonseasonal depression ...” (p. 20) and concluded that more research should be done in this area.<sup>72</sup>

LBT has also been demonstrated to be effective in depressed pregnant women. Oren *et al.*<sup>73</sup> conducted an open label trial of bright light therapy in an A-B-A design

**Table 1.** *Alternative Treatments for Depression in Pregnancy*

Treatment	Evidence in Nonpregnant Population	Evidence in Peripartum Population	Evidence in Prevention of Relapse
Psychotherapy	Strong evidence base for numerous types of therapy.	IPT is best studied and shows efficacy in the postpartum population. Partner Assisted IPT shows promise. More rigorous studies needed.	Some evidence for IPT.
Exercise	Minimal literature overall but several studies support the use of exercise in MDD.	One study showed a reduction in depressive symptoms in pregnant women with no psychiatric history.	One study found that exercise reduced relapse better than medication in MDD.
Light Box Therapy	Multiple studies support LBT use for SAD. There are mixed but overall positive results in nonseasonal MDD.	One open label and 2 randomized trials demonstrated support in depressed pregnant women.	No evidence.
rTMS	Strong evidence base for treatment of treatment-resistant depression.	Case reports and open label studies show benefit.	Clear support in the literature though exact protocols are unclear.
ECT	Strong evidence base for treatment of MDD.	Good evidence for use in appropriate peripartum patients.	Good evidence for efficacy in treatment resistant populations.
Acupuncture	Mixed results in the treatment of MDD. More rigorous study is needed.	One randomized trial in pregnant women demonstrated benefit. One study in PPD was negative.	No evidence.
Omega-3 Fatty Acids	Mixed results, efficacy likely depends on percentage of EPA versus DHA contained in preparation; other studies suggest no improvement.	Mixed outcomes ranging from no change to significant decreases in HAM-D, EPDS and BDI scores.	No evidence.
SAM-e	Several controlled trials indicate that parenteral administration is more efficacious than placebo in treating MDD.	No known controlled trials but “psychological distress” during the peripartum period was alleviated with supplementation during and after pregnancy.	No evidence.
Vitamin D	Improvement in depression scales at high doses.	No clear role for supplementation but low levels have been associated with depression.	No evidence.
Folate	Beneficial when used as augmentation with antidepressants.	Overall, studies show no significant changes in depression rating scales when used during the peripartum period.	No evidence.
St. John’s Wort	Mixed efficacy in several controlled trials.	Some improvement in depressive symptoms but additional safety and efficacy trials needed.	No evidence.

IPT: Interpersonal Therapy; MDD: Major Depression; LBT: Light Box Therapy; SAD: Seasonal Affective Disorder; DHA: docosahexaenoic acid EPA: eicosapentaenoic acid; BDI: Beck Depression Inventory; EPDS: Edinburgh Postnatal Depression Scale; HAM-D: Hamilton Depression Rating Scale

in 16 pregnant patients with MDD who were depressed. They found that mean depression ratings improved by 49%.<sup>73</sup> There have been two randomized trials of LBT in antepartum depression. Epperson *et al.*<sup>74</sup> found that women randomized to LBT (10,000 lux) had a 60% improvement in depression ratings compared to 41% in the placebo group (500 lux). The difference was not statistically different in this small sample ( $n = 10$ ).<sup>74</sup> A larger randomized trial of LBT (10,000 lux) in comparison to sham LBT (70 lux red light) in 27 depressed pregnant women found that LBT was superior, with 81% of the LBT sample responding versus 45% of the placebo group.<sup>75</sup> No studies have examined the role of LBT in the maintenance of remission in patients, either pregnant or nonpregnant, with mood disorders.

### *Repetitive transcranial magnetic stimulation*

Repetitive transcranial magnetic stimulation (rTMS) delivers a focused magnetic pulse to specific areas of the cerebral cortex.<sup>76</sup> It is currently approved by the U.S. Food and Drug Administration for treatment in adults with MDD who have failed at least one antidepressant trial in the current depressive episode.

A few case reports and open label studies have provided insight into the utility of rTMS in treating depression in pregnant women.<sup>77–81</sup> In one open label study, Kim *et al.*<sup>81</sup> administered 20 daily sessions of rTMS, each lasting for 10 minutes and targeted to the right dorsolateral prefrontal cortex, in 10 pregnant women with MDD who were clinically depressed. In this study, 70% of the patients responded to treatment, and 30% met criteria for remission. One limitation of the study is that some subjects were on antidepressants during the trial. However, there was no difference in response between groups based on medication status. In addition, no adverse pregnancy or fetal outcomes were reported.<sup>81</sup>

The benefits of using rTMS to treat major depression during pregnancy include a minimal side effect profile, good tolerability, and decreased fetal exposure to medications. In general, side effects from rTMS are only mild to moderate in intensity.<sup>82</sup> Similarly, when rTMS was used to treat depression in pregnancy, fetal heart rate was not affected by the treatment, and there were no adverse outcomes of the fetus, including changes in intrauterine growth or gestational period.<sup>81</sup> rTMS is also well-tolerated during pregnancy, and the majority of subjects who were enrolled completed their trials.<sup>79,81</sup> Finally, another benefit of rTMS in treating depression during pregnancy is that it eliminates fetal exposure to medication side effects and toxicity.

There are also some potential risks and limitations to the use of rTMS to treat a major depressive episode during pregnancy. One risk is that, because this

treatment is still very new, no long-term data are available on the effects of TMS on children born to women exposed to this intervention. A second risk is that it is unknown if pregnancy, specifically changes in circulating reproductive hormones, alters the efficacy of the treatment. A third risk is that, although the side effect profile is, in theory, relatively mild, headache and the theoretical risk of seizures may be a deterrent for some patients. Finally, recent studies have implemented anywhere from 10 consecutive days of treatments to 4–6 weeks of treatment every 2–3 days.<sup>83</sup> The frequency of treatments may also be a limitation for some people that cannot attend appointments as regularly as recommended for successful treatment. It remains to be tested whether the use of rTMS as a prevention or maintenance strategy is effective, and whether the frequency of treatments can be reduced in that setting.

### *Maintenance electroconvulsive therapy (ECT)*

The practice of ECT is well established as an effective and safe treatment for acute episodes of severe MDD and bipolar depression.<sup>84,85</sup> The use of ECT as a maintenance therapy in patients who have failed multiple medication trials but have responded to ECT has also been demonstrated, though specific guidelines for when it should be instituted are currently lacking.<sup>86,87</sup> ECT has been used successfully during pregnancy, and in some cases is used preferentially, particularly when the mother has had successful ECT in the past.<sup>88</sup> There are currently no case reports or trials of the use of maintenance ECT in a woman who was previously well on antidepressants and who wished to prevent relapse during pregnancy. While the use of maintenance ECT as a preventative strategy during pregnancy is certainly feasible, there are a number of disadvantages, including the use of anesthesia and the unestablished frequency of treatments. Many practitioners would likely feel that the use of ECT in any but severe cases is unwarranted.

### *Alternative "holistic" interventions*

Two recent Cochrane reviews concluded that the evidence for alternative "holistic" treatments such as massage therapy, acupuncture, and hypnosis for treating or preventing antenatal depression is currently inconclusive, and that the available randomized trials have been small and few and have lacked rigorous design methods.<sup>89,90</sup> Both reviews noted that the lack of rigorous research in this area was surprising, given the need for nonpharmacological treatments and prevention strategies for antenatal depression.<sup>89,90</sup> These types of interventions are often attractive to women with mood disorders who are contemplating

pregnancy, as they can be done conveniently and intermittently and do not require a daily or necessarily frequent commitment. However, given the lack of evidence supporting their use, they can really only be recommended as adjunctive treatments at this time.

There is one randomized trial of acupuncture in 150 pregnant women who met criteria for MDD in which women were randomized to acupuncture, control acupuncture, or massage therapy for 8 weeks.<sup>91</sup> Those who received acupuncture specific for depression experienced a greater reduction of depressive symptoms compared to control groups and had a significantly different (positive) response rate.<sup>91</sup> However, a more recent study of electroacupuncture for postpartum depression did not find significant differences between the active acupuncture group and the sham group, though the study was complicated by a small sample size.<sup>92</sup> There have been no studies examining the use of acupuncture as a prevention or maintenance treatment during pregnancy.

### *Nutritional and herbal supplements*

Nutritional and herbal supplements that have been explored as potentially useful agents in the treatment of perinatal depression include omega-3 polyunsaturated fatty acids, S-adenosylmethionine (SAM-e), 25-hydroxyvitamin D (vitamin D), folate, and St. John's wort. Although most have been found to have some utility in treating major depression in nonpregnant patients, overall there have been mixed results in efficacy in treating peripartum depression. An excellent review of this area by Freeman.<sup>93</sup>

Meta-analyses of randomized controlled trials of omega-3 polyunsaturated fatty acids in mood disorders indicate a statistically significant antidepressant effect, but there is overall a lack of consistency in study results and large heterogeneity in study designs.<sup>94,95</sup> Trials investigating the role of omega-3 fatty acids in perinatal depression have also demonstrated mixed efficacy, but some have shown decreases in depression rating scales.<sup>96,97</sup> Better trials with optimal doses and larger sample sizes are warranted.

Initial studies indicate that treatment/supplementation with SAM-e may alleviate depressive symptoms, and the Agency for Healthcare Research and Quality has indicated that further studies regarding its role as an antidepressant are warranted. However, its role in treating perinatal depression remains unclear, largely because it has not been studied in detail, though there is evidence suggesting a beneficial role in relieving "psychological distress" during the peripartum period.<sup>98</sup>

Numerous studies have shown an improvement in depression when patients are supplemented with high-dose vitamin D,<sup>99,100</sup> but results are still mixed since

other studies have not shown any improvement.<sup>101,102</sup> In peripartum depression, low levels of vitamin D have been associated with depression, but more studies are needed to determine the role of supplementation in treating depressive symptoms in this population.<sup>103</sup>

A role for the use of folate as an augmentation agent in conjunction with antidepressants has been established in nonpregnant patients,<sup>104</sup> but no significant changes in depression rating scales during the peripartum period were observed in a recent study, although some benefit was demonstrated in the postpartum period.<sup>105</sup>

St. John's wort, an over-the-counter supplement, has also shown mixed efficacy in the treatment of major depression.<sup>106,107</sup> Studies in the treatment of peripartum depression with St. John's wort have demonstrated some improvement, but both safety and efficacy trials are still needed.<sup>108</sup>

Overall, nutritional supplements show a significant amount of promise in both their efficacy as alternatives to "typical" antidepressants, as well as supplementation/augmentation with antidepressant therapy. However, further studies are warranted to investigate their safety and efficacy profiles before they can be considered mainstream treatment of peripartum depression.

### **Conclusions**

The management of mood disorders during pregnancy is complex. Treatment decisions are usually made based on the individual's history and the patient's preferences. Antidepressant use during pregnancy is an exposure for the unborn child, and it currently remains unclear what long-term repercussions there might be from this exposure, though available data are reassuring. There are increased risks of antidepressant use during pregnancy, including miscarriage, preterm birth, low birth weight, and possibly a very small increased risk for persistent pulmonary hypertension. The most common risk is the development of PNA syndrome in the newborn postpartum, though the significance of this syndrome remains unclear. On the other hand, there are risks for both the mother and child of untreated depression during pregnancy. Available data indicate that untreated depression during pregnancy is also associated with low birth weight and preterm birth. Mothers who are depressed during pregnancy are more likely to smoke and have other unhealthy habits. Antepartum depression increases the risk of postpartum depression, which has been demonstrated repeatedly to have significant effects on the exposed child's language development, IQ, and behavior. There is a real need for research into nonpharmacological strategies for the prevention of relapse of mood disorders in pregnant women who go

off medications during pregnancy. We have reviewed a number of potential candidate interventions, including psychotherapies, holistic treatments, exercise, LBT, rTMS, ECT, and nutritional supplements. Currently there is a lack of evidence supporting the use of such strategies in the prevention of relapse during pregnancy, though most of these strategies have support for their use in the treatment of a major depressive episode. Carefully conducted research using one or more of these strategies in women who want to discontinue antidepressants for pregnancy is sorely needed.

### Disclosures

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