# Complementary Health Practices for Treating Perinatal Depression



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## **KEYWORDS**

- Complementary Treatment Nutraceuticals Physical activity Yoga
- Depression 
   Postpartum 
   Perinatal

## **KEY POINTS**

- This review examines the evidence regarding common complementary health practices, including natural products (omega-3 fatty acids, folate, vitamin D, selenium, zinc, magnesium, B vitamins) and mind-body practices (physical activity interventions, yoga) in reducing perinatal depression.
- Current evidence regarding efficacy, safety, dosing, and duration of complementary health practices remains limited, yet promising data are emerging regarding the potential depression-reducing effect of omega-3 fatty acids, folate, vitamin D, physical activity, and yoga.
- Adequately powered high-quality studies are necessary to determine the role of complementary health practices for treating perinatal depression.

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# INTRODUCTION

Approximately 14% to 23% of women develop depression during pregnancy and up to 16.7% develop depression within 3 months postdelivery.<sup>1</sup> Perinatal depression (PND) is underdiagnosed and few women receive treatment.<sup>2</sup> Untreated PND is associated with functional impairment and adverse health outcomes for mother and child, including obstetric and neonatal complications<sup>3</sup> and a broad negative impact on child development.<sup>4</sup> Maternal suicide is the leading cause of maternal death occurring within 1 year postpartum.<sup>5</sup> Fortunately, safe and effective treatment options exist, including psychotherapy<sup>6</sup> and antidepressants.<sup>7</sup> However, an understanding of complementary health practices (CHPs) is important, because perinatal women may inquire about nonpharmacologic treatments.

CHPs include a diverse range of practices that are developed outside of mainstream Western medicine. Most CHPs fall into two categories: natural products or mind and body practices. Natural products, including herbs, vitamins, minerals, and probiotics, are the most widely used CHP in the United States. Mind and body practices include techniques that are typically administered or taught by a practitioner. Physical activity interventions may also be conceptualized as a form of CHP.

In general, women suffer from disorders, such as depression and anxiety, more often than men, for which CHPs are commonly pursued.<sup>8</sup> Despite growing popularity of CHP, research is limited. In light of their increased use, we reviewed literature on CHPs for PND. We included specific approaches (ie, omega-3 fatty acids [O-3FA], folate, vitamin D, selenium, zinc, magnesium, B vitamins, physical activity, yoga) based on prevalence of use and availability of evidence from randomized controlled trials (RCT) in PND. In the absence of RCT evidence in PND, we included data from nonrandomized trials and studies addressing impact of these approaches on depressive symptoms within nonclinical populations.

#### NATURAL PRODUCTS Omega-3 Fatty Acids

O-3FA are one of the most popular CHPs used in the United States. O-3FA are essential polyunsaturated fatty acids with well-established health benefits.<sup>9</sup> Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two important O-3FAs. Guidelines recommend pregnant women consume at least 200 mg/d of DHA.<sup>10</sup> The 2015 to 2020 Dietary Guidelines for Americans<sup>11</sup> and the American College of Obstetricians and Gynecologists (ACOG) recommend pregnant or breastfeeding women consume 8 to 12 ounces of seafood weekly, which provides approximately 250 mg/d of EPA and DHA.<sup>12</sup>

Meta-analyses of RCTs suggest antidepressant benefits of O-3FA in mood disorders overall, but there has been heterogeneity in study design, quality of evidence, and results.<sup>13,14</sup> O-3FA have been studied as augmentation to treatment<sup>15</sup> and as depression monotherapy.<sup>16</sup> The American Psychiatric Association recommends patients with a mood disorder consume 1 g/d EPA + DHA.<sup>17</sup>

Studies on the relationship between serum O-3FA levels or dietary seafood intake and PND have yielded mixed results.<sup>18,19</sup> In a large prospective Danish cohort study including more than 54,000 women, those with the lowest quartile of fish intake were at increased risk of antidepressant treatment postpartum.<sup>20</sup> Several RCTs assessing O-3FA supplementation in the treatment or prevention of PND have not demonstrated benefit.<sup>21</sup> A large double-blind RCT including 2,399 nondepressed pregnant women who received either 800 mg/d DHA plus 100 mg/d EPA or vegetable oil during the last half of pregnancy<sup>22</sup> showed no between-group difference in PND symptoms as measured by the Edinburgh Postnatal Depression Scale (EPDS).<sup>22</sup>

Three double-blind placebo-controlled RCTs in depressed pregnant women found a significant benefit of O-3FA as monotherapy for antenatal depression.<sup>23–25</sup> Another trial, however, did not find any benefit compared with placebo in pregnant women at high risk for PND.<sup>26</sup> A recent systematic review and meta-analysis of 12 studies noted lower levels of EPA and DHA were associated with PND.<sup>19</sup> Given some positive findings from RCTs and meta-analyses in depression and PND, we recommend depressed perinatal women consume 1 g/d EPA + DHA in addition to psychotherapy or pharmacotherapy as recommended by their behavioral health clinician. Further high-quality studies are needed to determine optimal dose and treatment duration. Please see Table 1 for a summary of research on natural products.

#### Folate

Folate exists in several forms, including folic acid, folinic acid, and the biologically active 5-methyltetrahydrofolate and participates in the production of nucleic acids and amino acid metabolism. Folate is converted to L-methylfolate, a biologically active form. Folic acid and folinic acid are synthetic forms of dietary folate and require methylenetetrahydrofolate reductase (MTHFR) to be converted into biologically active forms. Polymorphism of MTHFR is common in depressed patients, resulting in impaired transformation of folate to L-methylfolate. Pregnant women and women with the potential for pregnancy are recommended to consume 0.4 to 0.8 mg of folic acid daily.<sup>27</sup> Women at elevated risk for delivering an infant with a neural tube defect are advised to consume 4 mg/d folic acid before and during pregnancy.<sup>27,28</sup>

Studies report an association between low folate and an increased risk of depression.<sup>29</sup> Synthetic forms of dietary folate and L-methylfolate have been tested as adjunctive treatment in depression,<sup>30</sup> but results are inconsistent.<sup>31</sup> No published trials have examined the efficacy of folate monotherapy or augmentation therapy for PND.<sup>32</sup> Epidemiologic data generally do not demonstrate that higher folate intake during pregnancy mitigates PND<sup>33</sup>; however, in one study of 709 pregnant women,<sup>34</sup> lower plasma folate status was associated with antenatal depression. A prospective study of 6,809 women reported that antenatal folic acid supplementation protected against PND; this was especially evident in those with the MTHFR C677T genotype.<sup>35</sup> Another study of 1,592 women found that 6 months of folate supplementation was associated with lower rates of PND.<sup>36</sup>

In summary, in perinatal women with low serum folate levels, folic or folinic acid supplementation carries little risk and may reduce PND risk. However, given lack of clear evidence, it is premature to conclude that doses higher than that recommended by ACOG are effective in PND treatment.

### Vitamin D

Vitamin D is a fat-soluble vitamin available as a biologically inert dietary supplement and produced endogenously by the skin after sunlight exposure.<sup>37</sup> 25-hydroxyvitamin D (25-(OH)-D) is the product of the first hydroxylation of vitamin D. The US Recommended Dietary Allowance (RDA) for vitamin D intake during pregnancy and during lactation is 600 IU/d (15  $\mu$ g). Prenatal vitamins generally contain 400 IU but greater supplemental doses of 1500 to 2000 IU/d of vitamin D may be needed to obtain serum concentrations greater than 30 ng/mL.<sup>38</sup>

Data support a lower risk of subsequent depression with higher serum levels, between 50 and 85 nmol/L.<sup>39</sup> A meta-analysis of observational studies involving 31,424 nonpregnant adults reported low vitamin D levels associated with clinical depression.<sup>40</sup> Recent RCTs report conflicting results.<sup>41</sup> One meta-analysis found an effect size for vitamin D comparable with that of antidepressants,<sup>42</sup> but other meta-analyses did not find a significant reduction in depression in nondeficient patients.<sup>43</sup>

Many studies report lower maternal 25(OH)-D levels to be associated with PND.<sup>37,44</sup> Observational studies identify an association between higher dietary vitamin D intake and a lower prevalence of PND symptoms.<sup>45,46</sup> In contrast, another study including 875 unaffected and 605 women with PND reported serum levels above sufficiency were associated with an increased risk of PND.<sup>47</sup>

To date, only one RCT has assessed efficacy of vitamin D as a treatment of PND. That study reported that 2000 IU/d for at least 8 weeks starting at the onset of the third trimester was associated with reduced depression in late gestation and 8 weeks postpartum, compared with placebo plus typical prenatal vitamins.<sup>48</sup> This study's generalizability is unclear because women with moderate-severe depressive symptoms (ie, EPDS >13) were excluded and nearly 70% of the women were vitamin D deficient.

Vitamin D deficiency should be promptly treated to reduce maternal, fetal, and neonatal health risks associated with deficiency. Treatment of vitamin D deficiency may lower the risk of PND. Larger trials need to be conducted before routine use of vitamin D is recommended for use in nondeficient pregnant women at risk for developing PND.

# OTHER NUTRACEUTICALS, MICRONUTRIENTS Selenium

Selenium is an essential trace element present in many foods like seafood, meat, and breads. The RDA of selenium is 60  $\mu$ g in pregnancy.<sup>49</sup> Low selenium intake is associated with increased risk for depression.<sup>50</sup> Outcomes of intervention trials have been mixed.<sup>51,52</sup> One RCT investigated selenium supplementation for the prevention of PND.<sup>53</sup> This double blind, placebo-controlled study enrolled 166 healthy first-trimester women. Women received either placebo or 100  $\mu$ g/d selenium yeast for 6 months until delivery. The mean postpartum EPDS score in the selenium group was lower than that of the control group but the result was not statistically significant.<sup>54</sup>

A large naturalistic prospective study of 475 pregnant women investigated the relationship between risk for PND symptoms and use of several micronutrient supplements, including B vitamins, vitamin D, iron, magnesium, selenium, zinc, and O-3FA.<sup>55</sup> Only selenium use greater than RDA levels reduced the odds of scoring as probable minor depression on the EPDS.

Currently, there is insufficient evidence to conclude that prenatal selenium supplementation prevents or treats PND. High-quality controlled clinical trials should be conducted to determine if selenium supplementation could have a role in the prevention or treatment of PND.

### Zinc

Zinc is an essential element required as a cofactor of many enzymes; it is found in red meat, poultry, and beans. The RDA during pregnancy is 11 mg<sup>56</sup> and pregnant women should not take more than 40 mg/d. Studies have reported lower serum zinc concentrations associated with depression,<sup>57</sup> including PND.<sup>58</sup> Several trials have investigated zinc as an adjunct to antidepressants.<sup>59</sup>

Few studies to date have focused on perinatal women and current results are mixed.<sup>55,60</sup> A recent RCT evaluated the effects of zinc sulfate versus magnesium sulfate supplementation versus placebo in preventing PND symptoms and anxiety.<sup>61</sup> This

study included 99 healthy early postpartum women. Both supplements were tolerated, but no significant difference in symptoms was found 8 weeks postpartum.

Well-designed placebo-controlled RCTs with zinc in PND are limited. Zinc has potential benefit regarding mood but can interact with medications including antibiotics.<sup>62</sup> At this time zinc cannot be recommended to prevent or treat PND.

## Magnesium

Magnesium is a trace mineral that activates many enzymes. The RDA in pregnancy ranges from 360 mg to 400 mg.<sup>63</sup> No clear association between magnesium deficiency and depression has been reported.<sup>64</sup> Few studies to date have focused on perinatal women and current results are mixed as reviewed previously.<sup>55,61</sup> At this time, there is insufficient evidence supporting perinatal magnesium supplementation to treat depression, particularly given the potential interactions with other medications.

#### **B** Vitamins

B vitamins function as important coenzymes or the precursors needed to make coenzymes, for metabolic processes. The RDA of riboflavin (B<sub>2</sub>) during pregnancy is 1.4 mg. The RDA of pyridoxine (B<sub>6</sub>) in pregnancy is 1.9 mg; pregnant women should not take more than 80 mg/d.<sup>65</sup> The RDA of cobalamin (B<sub>12</sub>) during pregnancy is 2.6  $\mu$ g.<sup>66</sup>

A few studies support an inverse relationship between riboflavin (B<sub>2</sub>) intake and depressive symptoms<sup>67</sup>; however, sparse research exists with perinatal women. A prospective cohort study using self-reported dietary intake in 865 pregnant women suggested that consuming food with high riboflavin content was associated with a decreased PND risk.<sup>68</sup>

Deficiency in pyridoxine (vitamin  $B_6$ ) and cobalamin (vitamin  $B_{12}$ ) is associated with increased homocysteine, a proinflammatory amino acid. Studies investigating the association between pyridoxine and depression report inconsistent findings.<sup>69,70</sup> Cobalamin deficiency has been associated with non-PND<sup>71</sup>; however, no clear association has been documented between cobalamin and PND.<sup>32</sup> A few studies have reported a lack of correlation between perinatal plasma cobalamin levels or intake and PND.<sup>34,68</sup> A large study of 905 women with postpartum depression symptoms and 1,951 without symptoms similarly did not find any relationship between depressive symptoms and dietary intake of folate, cobalamin, or pyridoxine at 6 months or 1 year postpartum.<sup>72</sup> Overall, there is insufficient evidence to recommend riboflavin, pyridoxine, or cobalamin supplementation for PND.

## MIND AND BODY PRACTICES Physical Activity

Regular physical activity is an important part of maintaining health and a sense of well-being. A growing literature documents mental health benefits of exercise including increased activity as a strategy for lowering depression. Behavioral, psychological, and physiologic mechanisms have been proposed to explain the mood-enhancing effect of exercise. In contrast to older recommendations to minimize perinatal exercise, ACOG currently endorses regular physical activity (ie, 20–30 minutes daily of moderate intensity activity) among healthy pregnant and post-partum women, and observational studies document numerous benefits of perinatal exercise. In light of potential benefits to overall health and mood, tailored exercise programs have been suggested as promising strategies for improving maternal perinatal mood.

Table 1           Natural products as treatments for perinatal depression: current evidence and recommendations	
Natural Product	Recommendation for Use During Pregnancy and Postpartum
Omega-3 fatty acids	<ul> <li>Evidence suggests daily EPA + DHA is well tolerated and may help reduce depression during perinatal period</li> <li>Consistent with APA guidelines, a daily dose of 1 g/d of EPA + DHA is recommended to help reduce depression, as an adjunct to standard mental health treatment</li> </ul>
Folate	<ul> <li>Modest support currently exists for an antidepressant effect of folate augmentation in nonperinatal populations, with little evidence of risk</li> <li>ACOG recommends 600 µg of folate daily to reduce risk of neural tube defects. Adhering to this dose is important for fetal health and may also help reduce maternal depression, particularly in women with low serum folate levels</li> </ul>
S-adenosyl-L- methionine	<ul> <li>No RCTs to date with depressed pregnant women; only one study has examined S-adenosyl-L-methionine for postpartum depressive symptoms</li> <li>Currently not enough evidence regarding efficacy and safety to recommend S-adenosyl-L-methionine for perinatal depression</li> </ul>
Vitamin D	<ul> <li>Only one RCT has examined vitamin D as a treatment of perinatal depression</li> <li>Treating vitamin D deficiency is critical for maternal-child health; however, there is currently insufficient evidence to recommend vitamin D for perinatal depression in nondeficient women</li> </ul>
Selenium	<ul> <li>No RCTs have evaluated selenium as a treatment of perinatal depression; one RCT has examined preventative effect</li> <li>Currently not enough evidence regarding efficacy to recommend selenium as a treatment of perinatal depression.</li> </ul>
Zinc	<ul> <li>No RCTs have evaluated zinc as a treatment of perinatal depression; one RCT examined preventative effect</li> <li>Currently not enough evidence regarding efficacy to recommend zinc as a treatment of perinatal depression</li> </ul>
Magnesium	<ul> <li>No RCTs have evaluated magnesium as a treatment of perinatal depression; one RCT examined preventative effect</li> <li>Currently not enough evidence regarding efficacy to recommend zinc as a treatment of perinatal depression</li> </ul>
B vitamins	<ul> <li>No RCTs have evaluated B vitamins as treatments of perinatal depression</li> <li>Currently not enough evidence regarding efficacy to recommend riboflavin, pyridoxine, or cobalamin for perinatal depression</li> </ul>

Although exercise has been tested as an intervention for depression in numerous studies in the general population, only a few trials have examined the effects of exercise among depressed perinatal women. Six RCTs have examined various forms of exercise for postpartum women with depression symptoms, and one open trial has examined an exercise intervention for depressed pregnant women.

Among the RCTs examining exercise for PND, the type of exercise intervention has varied, including group-based pram-walking,<sup>73</sup> facility-based group exercise,<sup>74</sup> and individualized exercise interventions tailored to participant needs and preferences.<sup>75,76</sup> The amount of physical activity promoted by these programs and duration has also varied, yet all involved mild-moderate intensity levels of activity and exertion. With one exception,<sup>73</sup> comparison conditions have involved no-treatment control groups. Findings regarding efficacy are generally encouraging, yet not all studies

yielded positive findings. Two RCTs<sup>73,74</sup> found the exercise group experienced greater depression reductions than the control group; this includes a small trial (N = 19) that found that a twice-weekly pram-walking intervention was more effective than weekly social support for improving mood, and a larger study (N = 80) that found greater symptom reduction among women who participated in a group/individual exercise program versus standard care. In a later trial with 94 postpartum women, Daley and colleagues<sup>76</sup> documented greater depression reduction in an exercise group; however, differences were small and not maintained at 12-month follow-up. Da Costa and colleagues<sup>75</sup> reported no differences between exercise and control groups, yet additional analyses revealed that women with high baseline depression scores did experience significant depression reductions compared with women with high scores assigned to the control condition. Finally, two other RCTs<sup>77,78</sup> did not find an effect of group assignment on depression outcomes, one<sup>77</sup> noting that problems with adherence to the exercise intervention may have accounted for lack of effect.

In terms of prenatal interventions, only one small study has examined an exercise program for pregnant women with depression. In a nonrandomized trial with secondand third-trimester pregnant women, Battle and Abrantes<sup>79</sup> found clinically significant depression reductions and increases in physical activity following a 10-week lifestyle physical activity intervention. This intervention is currently being tested in a larger RCT (NCT02474862; clinicaltrials.gov).

Research on physical activity as a treatment of PND is new, and studies to date have been limited by small samples and lack of comparison groups that control for time, attention, and other concurrent depression treatment. Moreover, few trials have used objective physical activity measurement (eg, accelerometry, the gold standard in exercise research). Still, current evidence suggests that physical activity approaches are viewed as acceptable by perinatal women and providers, and no safety concerns have been documented. ACOG already recommends regular moderate-intensity physical activity among perinatal women and suggests that prenatal care providers should actively encourage their depressed patients without medical contraindications to adhere to these guidelines, because regular exercise may promote better mental and obstetric health. Providers should regularly assess patients' activity over the perinatal period to gauge ongoing safety and difficulties overcoming barriers to activity. Given the strong evidence for acceptability and potential for improving maternal health and mood, additional high-guality studies are needed to establish whether exercise interventions are efficacious as a treatment of PND, to clarify the optimal dose of exercise, and examine effective strategies for promoting adherence. Please see Table 2 for a summary of research on physical activity and yoga interventions.

#### Yoga

Yoga is an ancient practice that varies in style, yet typically combines three components: (1) physical postures, (2) breath control, and (3) meditation. A growing proportion of the United States and Canadian population practices yoga, and its popularity is higher among women than men. In recent decades the impact of yoga on physical and mental health has been examined (eg, to improve cardiovascular health, reduce pain). In light of putative mechanisms by which yoga could improve depression, yoga has been tested as a potential intervention for depression in the general population. This literature suggests that yoga is more effective in treating depression than placebo and comparable with aerobic exercise and antidepressant medication, despite methodologic limitations in studies to date.

Recently, prenatal and postpartum yoga have been studied as potential interventions to treat depression. Depressed pregnant women have found prenatal yoga to be acceptable, feasible, and safe.<sup>80-82</sup> In terms of open trials, one study examined a yoga program for depressed pregnant women and found significant decreases in depression via self-report and observer-rated measures.<sup>80</sup> Another trial reported significant reductions in depressive symptoms following a yoga program in a mixed patient sample with a range of symptoms.<sup>83</sup> RCTs of yoga for PND have compared brief yoga (or yoga/tai chi) programs with a range of conditions including waitlist.<sup>84</sup> massage and treatment as usual,<sup>85</sup> social support,<sup>86</sup> and parenting education,<sup>87</sup> reporting greater reductions in depressive symptoms in yoga versus waitlist, treatment as usual, and parenting education, and similar reductions versus massage and social support. These studies were conducted with diverse samples. Some studies were limited by use of a less typical style of yoga (eg, brief sessions with postures only), or reliance on self-report measures. Other RCTs have compared yoga programs with treatment as usual in depressed and/or anxious women<sup>82</sup> and a perinatal health education condition in depressed women,<sup>81</sup> and have reported decreases in depression, yet with minimal or no significant differences versus comparison conditions. One RCT examined a postpartum yoga intervention versus waitlist for women with depression up to 12 months postpartum and found that participants in the yoga condition reported greater improvements in depression.88

Although more research is needed, the existing body of research on prenatal and postpartum yoga is encouraging in terms of feasibility, acceptability, preliminary efficacy, and patient safety. Perinatal women without medical contraindications or activity restrictions may experience some mood benefit from a regular yoga practice tailored for perinatal women. The appropriateness of a yoga program should be assessed across the perinatal period, because medical status and activity restrictions may change. Rigorous, fully powered RCTs are needed to examine the efficacy of yoga for depressed women during pregnancy and postpartum, and explore questions of the adequate "dose" of yoga, and safety considerations. Future research should evaluate yoga interventions that are consistent with typical prenatal yoga classes offered in community settings, to maximize generalizability, and should use observer-rated measures of depression outcomes, in addition to self-report measures.

# SUMMARY

Given high levels of interest in CHPs during the perinatal period, there is a need for research addressing acceptability, safety, and efficacy of these interventions. Large-scale surveys suggest many perinatal women already seek out CHP for potential health benefits, even in the absence of clear safety and efficacy data, and a substantial subset of perinatal women report that their prenatal care providers do not ask about their use of CHPs.<sup>89</sup> As such, it is important for providers to routinely inquire about patients' interest in and use of CHPs, and additional research is needed to provide clear data to guide decisions about which products and practices are helpful and safe.

With a vast array of CHPs, we did not attempt to review evidence for all products or interventions. We examined data regarding some of the most commonly used CHPs, including various natural products and vitamins and popular mind and body approaches. Until subsequent research is conducted and questions answered, our review has found encouraging preliminary evidence supporting efficacy of O-3FA, folate, vitamin D (in cases of deficiency), physical activity interventions, and prenatal/postpartum yoga for reducing or preventing PND symptoms. However, some approaches have only been examined during pregnancy, and others only in the postpartum. At this time there is insufficient evidence for the efficacy of selenium,

449

Table 2           Physical activity and yoga as treatments for perinatal depression: current evidence and recommendations		
Mind or Body Intervention	Recommendation for Use During Pregnancy and Postpartum	
Physical activity	<ul> <li>Some evidence exists suggesting exercise may be efficacious in lowering postpartum depression without adverse effect; less evidence for antenatal depression, but positive results documented in one open trial.</li> <li>ACOG recommends moderate-intensity physical activity for 20–30 minutes on most days for pregnant women with uncomplicated pregnancies, and resuming (or starting) exercise when medically cleared postpartum.</li> <li>In addition to health benefits, following ACOG exercise guidelines may serve as an effective adjunct to standard mental health treatment to help improve mood among women with perinatal depression.</li> <li>Because of difficulty adhering to exercise programs while pregnant or postpartum, we recommend providers actively support women in increasing activity over the perinatal period to adhere to ACOG guidelines and obtain potential health and mood benefits.</li> </ul>	
Yoga	<ul> <li>Some evidence exists suggesting prenatal and postpartum yoga may be efficacious in lowering perinatal depression.</li> <li>Modified yoga is an activity recommended as "safe" by ACOG for women engaging in regular physical activity during pregnancy; guidelines note that "hot yoga" and postures that result in decreased venous return and hypotension should be avoided. No safety concerns have been documented with yoga interventions studied to date with perinatal women.</li> <li>A modified yoga practice is one strategy for adhering to ACOG physical activity guidelines, and preliminary evidence suggests that prenatal and postpartum yoga may also serve as an efficacious adjunctive intervention to help improve mood among women with perinatal depression.</li> </ul>	

zinc, magnesium, and B vitamins. Given their acceptability and availability, CHPs are an important area for future study to determine their utility as either adjunctive interventions or monotherapy to reduce PND.

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