POST-PARTUM DEPRESSION- TREATMENT UPDATE

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Abstract

Background: Postpartum depression is a prevalent and serious mental health issue in India. This affects not only a woman but also the development of her offspring. There is a need to find out various pharmacological and non-pharmacological treatment options available for the treatment post-partum depression.

Method: This review was based on methods and results as described in the selected published articles available on PubMed and PsycINFO. We identified articles whose titles contained the following key terms in various combinations of the following: depression, depressive illness, postpartum, postnatal, treatment, prevention, therapy, pharmacotherapy, and antidepressant, the name of each antidepressant drug, hormonal therapy, estrogen, and progesterone.

Results: We reviewed treatment of post-partum depression with antidepressants randomized clinical trials as well as open label studies, hormonal treatment, prevention studies randomized clinical trials as well as open label studies, alternative pharmacological treatment including omega-3- fatty acids- both for prevention and treatment. We also reviewed internet based intervention, cognitive behavioral therapy, kangaroo mother care, effectiveness of regular exercise, role of ECT and effect of rTMS in post part depression. When it's about safety, the psychological interventions support their use in some women, pregnant and lactating women because of devoid of side effects to new born.

Conclusion: Diverse pharmacological or psychological interventions options are available for treatment of postnatal depression. The most promising intervention is the focus on intensive and individualized approach.

Introduction

Specific female lifecycle periods of hormonal fluctuation (i.e., menstrual cycle, pregnancy, postpartum, and perimenopause) are consistently associated with depressive syndromes^[1, 2]. Post-partum depression (PPD) is the most common complication of childbearing, occurring in 10-15% of women after delivery. It usually begins within the first 4 weeks post-partum, women remain at increased risk throughout the first 5 months after child-birth^[2].

In May 2013, the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; *DSM-5*; American Psychiatric Association, 2013) was published with a modified specifier for major depressive episodes 'with peripartum onset'^[3]. Despite evidence that the time criterion should be expanded past 4 weeks postpartum^[4], the new DSM-5 specifier is used when the onset of depressive symptoms occurs during pregnancy or in the 4 weeks following delivery. The International Classification of Diseases, 10th Edition (ICD-10)^[5] includes "postpartum" or "postnatal depression NOS" among the mental and behavioral disorders associated with the puerperium (defined as beginning within 6 weeks after birth), not elsewhere classified.

Interestingly, while 40% of postpartum women with depression report the episode onset postpartum, 33.4% report antenatal onset and 26.5% report onset before pregnancy^[6]. Women with PPD are more likely to have future, recurrent depressive episodes compared to controls. In one longitudinal cohort study, women with PPD were six times more likely to experience future depressive symptoms than matched controls who did not suffer from PPD after childbirth^[7].

The following mechanisms are proposed for the development PPD:

1. Abrupt decrease in estradiol levels in postpartum period: During pregnancy, the brain is exposed to a 100-fold increase in ambient estradiol (E2) levels, which abruptly decrease in the first postpartum week^[8]. Researchers have suggested that the rapid change in gonadal steroid level, rather than the absolute level, is involved in the etiology of PPD. This hypothesis was supported by the work of Bloch et al^[9], who simulated the withdrawal of hormones after birth by inducing a hypogonadal state in women with leuprolide, adding back supraphysiologic doses of estradiol and progesterone for 8 weeks, and then withdrawing both steroids under double-blind conditions.

Five of eight women with a history of PPD, compared to none of the eight women without a history of depression, developed mood symptoms. Depressive symptoms peaked in the withdrawal (postpartum simulation) phase.

2. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis: There are also some empirical data to support the hypothesis that a dysregulation of HPA axis during pregnancy may predict a hyporesponsive HPA axis and depression during the postnatal period ^[10].

3. Genetic mechanisms: These mechanisms have been investigated as well. Women with serotonin gene polymorphisms may be at increased risk for depression in the early (< 8 weeks) postpartum period but conflicting results make these data premature for clinical use at this time ^[11, 12]. Women at risk for PPD may have an increased sensitivity to estrogen-based DNA methylation ^[13]. Two polymorphisms of the estrogen receptor α gene (ESR1) were strongly associated with PPD in another study ^[14], although replication in a larger sample is necessary for confirmation of these results.

PPD does not differ from depression at other periods during the childbearing years with respect to clinical presentation and duration of untreated episodes ^[15, 16]. However, aggressive obsessional thoughts occur more commonly in women who have PPD compared to those who have depression outside the one year postpartum time frame ^[17].

The recurrence rate of PPD has been estimated to be as high as 25% ^[18]. Its detrimental impact on the mother - infant dyad's health ^[19, 20] underlines the importance of prevention of both its occurrence to block the immediate post-birth cascade of events which result in PPD (primary prevention) and its persistence and worsening (secondary prevention). PPD provides an ideal opportunity for prevention because its onset is preceded by a clear marker (birth), there is a defined period of risk for onset, and a high-risk sample of mother can be identified ^[15].

There is a paucity of data in the literature regarding the efficacy of pharmacological treatment of PPD. The goals of this paper are to review the literature on the use of antidepressants and hormonal supplements for the prevention and the treatment of PPD. We will describe treatment studies that include the onset of depression in women through 12 months following birth.

Methodology:

An electronic search was performed by using PubMed and PsycINFO. We identified articles whose titles contained the following key terms in various combinations of the following: depression, depressive illness, postpartum, postnatal, treatment, prevention, therapy, pharmacotherapy, and antidepressant, the name of each antidepressant drug, hormonal therapy, estrogen, and progesterone. The search was not limited by any dates.

Inclusion criteria were: 1) empirical articles in peer-reviewed English language journals, 2) well validated measures of depression, and 3) uniform scoring system for depression among the sample. Relevant reviews were examined. This review was based on methods and results as described in the selected published articles.

3. Results:

The electronic search yielded a total of 23 articles. Of those, 16 articles were pertaining to treatment and included 8 randomized clinical trials (RCT) and 8 open-label studies. 7 prevention studies included 3 RCT and 4 open-label studies. Additionally, Six randomized controlled trials (RCTs) evaluating the use of omega-3 fatty acids (four for treatment Table 2 and two for prevention Table 3) have been published and are reviewed.

3.1. Antidepressant treatment studies-randomized clinical trials:

Appleby et al in 1997 ^[21] reported a very large effect size (2.4) for fluoxetine versus placebo after 4 weeks of treatment. Eighty-seven women with major or minor depressive disorder at 6–8 weeks after birth participated in a 12-week double-blind (for pharmacotherapy), randomized clinical trial with 4 treatment cells: fluoxetine (20 mg/day) or placebo plus one or six sessions of counseling derived from cognitive-behavioral therapy (CBT). Both fluoxetine and CBT were more effective than placebo in improving depressive symptoms. After an initial session of counselling, additional benefit resulted from either fluoxetine or further counselling but there was no advantage in receiving both. The choice of treatment may therefore be made by the women themselves. Since the baseline depression severity was mild (according to HAM-D score) the results of this study cannot be generalized to women with moderate to severe depression. Moreover, the outcome was limited to improvement in depressive symptoms.

Similarly, Misri et al. in 2004 ^[22] did not observe additional advantage in combining paroxetine with 12 sessions of cognitive behavior therapy in the treatment of PPD with comorbid anxiety disorders. In this 12-week randomized controlled trial, Thirty-five women were randomly assigned to 1 of 2 treatments groups-paroxetine-only monotherapy group (N = 16 and dose begun at 10 mg daily, individually tailored up to a maximum dose of 50 mg daily) or paroxetine plus 12 sessions of CBT (1-hour session weekly for 12 weeks) combination therapy group (N = 19). Both groups showed a highly significant improvement ($p < .01$) in mood and anxiety symptoms. Groups did not differ significantly in weeks of recovery, dose of paroxetine at remission, or measures of depression and anxiety at outcome. The major limitation of this study is the small sample size.

Wisner et al. (2006) ^[23] in an 8-week double blind RCT, compared symptom reduction and improvement in

functioning in women with postpartum major depression treated with a nortriptyline versus sertraline. This was followed by a 16-week continuation phase to test durability of response. Women aged 18 to 45 years with postpartum major depression and a 17-item Hamilton Rating Scale for Depression score of 18 or more were eligible. Subjects were randomized to NTP or SERT and treated with a fixed-dosing strategy. Of 420 women interviewed, 109 eligible women received medication, with 54 receiving nortriptyline and 55 sertraline. The proportion of women who responded and remitted did not differ between drugs at 4, 8, or 24 weeks. Times to response and remission also did not differ. For both drugs, over 75% of women who remitted by week 8 also met response criteria by week 4. Psychosocial functioning improved similarly in both drug-treated groups of mothers. The total side effect burden of each drug was similar, although side effect profiles differed between agents. No clinical or demographic variables differentiated responders by drug. Women who were responders and remitters at week 8 could be identified earlier if they were treated with SERT than with NTP. The dosages required to achieve remission after 8 weeks of treatment were: for the 25 sertraline-treated remitters: only 1 = less than 100 mg/d, 12 = 100 mg/d, 5 = 125 or 150 mg/d, and 7 = 200 mg/d; for 26 nortriptyline remitters: 15 = less than 100 mg/d, 7 = 100 mg/d, and 4 = 125 or 150 mg/d.

Yonkers et al. in 2008^[24] conducted an 8-week double-blind placebo-controlled randomized clinical trial in 70 women with onset of PPD within 3 months after birth. In this study, seventy women were randomly assigned to either immediate-release paroxetine or matching placebo, and 31 completed the trial. The rate of remission at 8 weeks (defined as HAM-D $\leq$ 8) was significantly higher in the paroxetine group compared to placebo (37% compared to 14%; $p = .04$). On the contrary, response rate at 8 weeks (defined as CGI = 1 or 2) was higher in the paroxetine group but did not achieve statistical significance (43% compared to 32% in the placebo group; $p = .94$). The dose of paroxetine did not differ in the responders compared to non-responders (22.9 mg/day $\pm$ 12.1 and 19.4 mg/day $\pm$ 9, respectively; $p = .34$). The major limitation of this study is the small sample size.

Sharp, 2010^[25] A randomized, 18-week trial compared antidepressants (various antidepressants, mostly SSRIs) prescribed by a general practitioner to general supportive care and listening visits by a trained research health visitor in 254 women. PPD onset was within 6 months postpartum. Women were randomized to medication or general supportive care for 4 weeks. After the acute phase, the listening visits were started and women could at any time choose to change or add the alternate treatment. Prior to trial entry, women reported a preference to be randomized to listening visits over medication. EPDS score was the main outcome. At 4 weeks, women were twice as likely to have responded (EPDS < 13) on antidepressants

compared to those randomized to listening visits, which was general supportive care for the acute phase (45 vs 20%, OR 3.4 [95% CI 1.8 – 6.5], $p < 0.001$). At 18 weeks, there was no difference between women originally randomized to medication versus listening visits but many women were receiving both interventions by study end. These data suggest that symptom improvement is more rapid in women who receive antidepressant treatment and that antidepressant medications may become acceptable to women who are initially resistant to pharmacotherapy.

Hantsoo 2014^[26] In a single-center, 6-week, randomized double blind trial of sertraline for 36 women with PPD, sertraline was significantly more effective than placebo. The trial design included a 1-week placebo lead-in. PPD was defined as a depressive episode that onset within 3 months postpartum with antenatal onset excluded. The participants were prescribed sertraline 50 mg or placebo daily to a maximum of 200 mg/day. Compared to women in the placebo group, a greater proportion of women in the sertraline group met study criteria for treatment response (59 vs 26%, $p = 0.05$). A *post hoc* analysis restricted to subjects with PPD onset within 4 weeks of childbirth showed an even larger differential in the proportion of responders between the antidepressant and placebo groups (50 vs 6.7%, $p = 0.02$). In this sample, women with earlier onset PPD had a shorter duration of illness and a greater incidence of past psychiatric diagnosis but this was not statistically significant. If confirmed in a larger sample, this may suggest that women with PPD onset acutely after childbirth, who develop depression in the context of neuro-active steroid withdrawal, may have a different disease course from those who develop PPD at later time points.

Bloch *et al.* 2012^[27] conducted a single-center, 8-week, randomized, double-blind placebo controlled study of sertraline add-on to brief dynamic psychotherapy (BDP) for women suffering mild-to-moderate (MADRS score < 30), first episode PPD. Episode onset was within 2 months postpartum. Sertraline titration was as follows: 25 mg for the first week, 50 mg for 3 weeks, then up to 100 mg for 4 weeks or kept at 50 mg based on the psychiatrist's decision. The mean sertraline dose at 8 weeks was 67.5 $\pm$ 21.5 mg. All patients received 12 weeks of BDP starting with the onset of the sertraline titration. Forty women were included in the primary 8-week intent-to-treat analysis. Two women in the active group became hypomanic at week 8. There was no statistically significant difference between groups although the response rate (50% or greater decrease on MADRS or EPDS) was 55% (placebo + BDP) vs 70% (sertraline + BDP) and remission rate (MADRS < 10 or EPDS < 7) was 50% (placebo + BDP) vs 65% (sertraline + BDP). The authors suggested that including women with more severe depression may have led to significant results based on data that shows that the benefits of antidepressants are more striking in more severely depressed populations. Other hypotheses raised

by the authors include the possibility that women with low E2 levels may be less medication responsive, that sertraline was dosed too low or that the small sample size may have also impacted the study results. The most likely hypothesis is that the sertraline dose may have been too low for some of the women as many women with PPD need higher doses of sertraline to achieve response [52]

3.2 Antidepressant treatment studies-open label studies:

Roy et al.^[28] reported 4 cases of moderate to severe PPD with onset within 12 weeks after birth. The women were treated with fluoxetine (20 mg daily) for 3 to 6 weeks. All subjects achieved recovery, defined as Hamilton Depression Scale (HAM-D) ≤ 7 or Clinical Global Impression Scale (CGI) = 1. The description of 4 single cases limits the generalizability of the results to the general population. Stowe et al.^[29] reported the efficacy of sertraline in a prospective open-label study of 26 women with moderate PPD onset within 24 weeks after birth. The dose was 50 mg/day for the first two weeks and increased to a maximum of 200 mg/day depending on depressive symptoms and tolerance. All women in the study also received supportive psychotherapy. By week 8, 14 subjects experienced recovery defined as HAM-D ≤ 7 or CGI = 1, and 20 subjects achieved response (defined as $>50\%$ reduction from baseline HAM-D scores). Definitive conclusions from this study are limited secondary to the open design, small sample size, and the use of concomitant psychotherapeutic interventions.

Cohen et al.^[30] reported data on an 8-week open label trial of venlafaxine in 15 women with severe PPD with comorbid anxiety (mean HAM-D at baseline = 26.13 ± 5.15). The mean dose of venlafaxine across the study was 162.5 mg/day (range 75–225). After 2 weeks of treatment, the subjects had a significant decrease in depression and anxiety symptoms, and the rate of remission at week 8 was 80% (defined as HAM-D ≤ 7 or CGI ≤ 2). The major limitations of this study were the small sample size and the lack of double-blind randomized design.

Suri et al.^[31] conducted an 8-week open label trial of the use of fluvoxamine for the treatment of PPD in 6 subjects with scores of ≥ 17 on the 21-item HAM-D and ≥ 12 on the Edinburgh Postnatal Depression Scale (EPDS). The fluvoxamine dose was initiated at 50 mg/day and titrated to 150 mg/day over the first 2 weeks. The mean final daily dose of fluvoxamine for all subjects was 142 mg/day ± 20 (150 mg/day for the three responders and both nonresponders and 100 mg/day for one responder). The rate of remission was 67% (defined as HAM-D ≤ 7) and the greatest degree of improvement occurred between weeks 2 and 3. The major limitations of this study were the small sample size, lack of randomized double-blind design. Moreover, the baseline HAM-D scores were not reported.

Nonacs et al.^[32] conducted a pilot study on the use of bupropion for the treatment of PPD. Eight women with

moderate PPD were enrolled in an 8-week open label trial using a flexible dosing schedule (median HAM-D at baseline = 20.5, range 15–38). Three women also had comorbid anxiety disorders. Dosage started at 150 mg/day and was adjusted at each visit to a maximum of 400 mg/day depending on side effects and depressive symptoms. The median effective dosage across the study was 262.5 mg (range 37.5–300 mg). Concomitant zolpidem (up to 10 mg) and lorazepam (up to 2 mg/day) were permitted. At the study end-point, 6 of the 8 patients (75%) achieved response and 3 achieved remission (37.5%). Response rates were similar of those found by Cohen et al.^[30] and Stowe et al.^[29] with venlafaxine and sertraline, respectively. However, the rates of remission were lower. Only a trend toward significant improvement in anxiety symptoms was observed and none of the 3 patients with PPD and comorbid anxiety disorder achieved remission. The small sample size and the open-label design limit the generalizability of the results.

All studies cited above were conducted among clinically significant depressed subjects and included antidepressants with different mechanisms of action (venlafaxine, bupropion). Only venlafaxine adequately treated both depressive and anxiety symptoms, which are common in women with PPD.

Fifteen women with PPD onset within 12 months of childbirth completed a 10-week open-label study of citalopram^[33]. Ninety-three percent of subjects were responders (50% or greater reduction in Montgomery–Asberg Depression Rating Scale [MADRS] scores). The mean number of weeks to remission (MADRS score of 10 or less) was 7.23 (SD 1.68). The citalopram was started at a dose of 10 mg and increased to 20 mg over 10 weeks based on subject ratings. The authors do not indicate why such a low dose of citalopram was chosen although in one subject the dose was increased to 40 mg and in another subject quetiapine was added, both for anxiety symptoms. The subjects in this study achieved improvement on a low SSRI antidepressant dose but it took almost 8 weeks for symptoms to remit. Open-label trials often have high response rates, so an RCT would be helpful to confirm these results.

3.3 Hormonal treatments of PPD:

There is continuing interest in the use of hormones for the treatment of PPD. In women, there are three estrogens: estrone (E1), E2 and estriol (E3). E2, the most potent of the bioestrogens, promotes neuronal growth and survival, is pro-serotonergic and decreases oxidative stress^[34]. Oral estrogens typically are conjugated equine estrogens with a predominance of E1^[35]. Of the bio-identical estrogens, 17- β -E2 has greater ESR affinity than E1 or E3^[36]. Transdermal 17 β -E2 bypasses hepatic metabolism and results in 1:1 ratio of E2 to E1. Since transdermal E2 avoids the induction of hepatic coagulation factor, it does not increase the risk of venothrombotic events as much as conjugated equine estrogens do. It also is more available to the brain. The risk

of endometrial cancer occurs in 1% of long-term estrogen users who develop endometrial hyperplasia due to not cycling the endometrium with progesterone. Although decreased milk production can occur, there is negligible passage of transdermal E2 for doses up to 100 mcg/day into breast milk^[37].

Gregoire et al^[38] randomized 61 women with severe PPD to placebo (N=27) or 17 β -estradiol (17 β -E2) (N=34) (200 mcg/day) delivered by transdermal patch for 6 months. The mean EPDS total score in the E2 group was 21.8 ± 3.0 , and in the placebo group was 21.3 ± 2.9 . The mean E2 concentration of actively treated women was 680 pmol/L (as a comparison, the mean E2 concentration across the menstrual cycle is 370 pmol/L). Both groups improved over time; however, the E2 treated group improved rapidly. The mean EPDS score for E2-treated subjects was <14) and was 4 points lower than that of the placebo group at study completion.

Symptomatic improvement in the E2 group was 2-fold higher than that of the placebo group. By 3 months of treatment, 80% of the E2 group but only 31% of placebo group had EPDS scores <14. Because assessments were done once a month, the time course of response in the early weeks of treatment is unknown. E2 treatment was well-tolerated as judged by low attrition. Endometrial changes were found in 3 participants at the study conclusion (6 months), despite co-administration of dydrogesterone (10mg/day, 12 days per month in the final 3 months of the E2 trial). The endometrial changes resolved at followup. The inclusion of women who took concurrent antidepressant medications (47% and 37% in the E2 and placebo arms, respectively) limits the ability to discern an E2-specific treatment effect. Moreover, the validity of the findings would be increased if they were confirmed with a clinician interview-based measure.

The studies of Gregoire et al^[38] and Ahokas et al^[39] suggest that E2 treatment is associated with a rapid and robust response in women with PPD. The recovery rate reported in both E2 trials was higher than that of standard antidepressants^[40]. Although symptom reduction was considered rapid in the E2 trials compared to that of antidepressants, the dictum that the response to an antidepressant response is delayed by many weeks was challenged by the findings of a meta-analysis^[41]. The authors selected 47 studies that included antidepressant medications with established efficacy, obtained weekly or biweekly assessments, and presented the time course of improvement as measured by the HAM-D. The greatest amount of improvement occurred during the first 2 weeks. Drug-placebo differences were not only present but were most pronounced during the first 2 weeks of treatment and diminished thereafter.

In a small study that looked at both animals and humans, E2 withdrawal was associated with anhedonia (behavioral despair) in rats but there was no association between E2

levels and negative affect in non-pregnant women is considered high risk for the development of PPD due to a previous history of PPD^[42]. However, in women who did develop PPD at 4 weeks postpartum, there was a negative association between daily perinatal salivary E2 levels and negative affect ($r = -0.34$, $p < 0.001$). Other studies have shown an association between depressed affect and E2 levels in women at risk for PPD (Bloch and Sacher). Although there is a current investigation underway of the efficacy of transdermal 17 β -E2 to replicate and extend a 1996 study by Gregoire et al.^[38], (personal communication Wisner), there are no new cases or studies published.

3.4. Prevention studies-randomized clinical trials:

Wisner et al^[18] tested the efficacy of the tricyclic antidepressant nortriptyline for the prevention of PPD recurrence in a double-blind randomized placebo-controlled clinical trial. The authors reported data from 51 women with at least one lifetime episode of major depression with postpartum onset. The subjects were recruited during pregnancy and randomly assigned to receive nortriptyline (N=26) or placebo (N=25) immediately after birth. For the first postpartum week, the dose was increased daily as follows (mg): 20,30,40,50,50,60,70 and continued at 75 mg/day through day 21, when it was adjusted based on the serum level from day 14. The drug was provided for 17 weeks to cover the high-risk period for PPD as defined by Kendell et al^[43] of 3 months, or 14 weeks. The drug was tapered starting at week 17 at a rate of 33% per week and was discontinued at 20 weeks postpartum. The mean serum drug level for nortriptyline (83 ng/mL) across the study period was within the usual therapeutic range for this drug (50 –150 ng/ml). The rate of recurrence of PPD did not differ between the two groups (23.5%=nortriptyline; 24%= placebo). The time to PPD recurrence ranged from 1 to 16 weeks and it also did not differ between the two groups. Contrary to the results of the previous open-label study conducted by the same author^[15], the efficacy of nortriptyline in the prevention of PPD recurrence was not confirmed by this randomized controlled study. As the authors pointed out, this difference may be due to the fact that women are more likely to respond to the treatment to which they have previously responded. The major limitation of this study is the small sample size.

In a second randomized clinical trial with the same protocol, Wisner et al^[44] demonstrated that sertraline conferred additional preventive efficacy beyond that of placebo (7% in the sertraline group versus 50% in the placebo group; $p=.04$). The authors reported data from 22 women (sertraline, N=14, placebo, N=8). The dosing protocol began with 25 mg/day of sertraline for 4 days, increased to 50 mg/day through week 4, then to 75 mg/day during weeks 5–17. At study week 17 the dose was tapered across 3 weeks, and treatment was discontinued at week 20. Serum levels were determined to assess

compliance. Interestingly, after sertraline was withdrawn (at week 20), 2 of the 9 women who completed the trial experienced PPD recurrence. This observation suggested that the vulnerability to experience PPD persists beyond the period of drug therapy and pharmacological treatment should be continued for more than 17 weeks. The authors recommended a minimum treatment period of 26 weeks, or about 6 months, which is consistent with American Psychiatric Association guidelines for the duration of treatment for a single episode of depression^[45]. The major limitation of this study is the small sample size. The positive results of this study are in contrast to the authors' results with the tricyclic antidepressant nortriptyline as the preventive agent. Consistently, serotonin selective reuptake inhibitors are effective compared to placebo for premenstrual dysphoric disorder, but nonserotonergic tricyclics are not. A possible explanation of this selective efficacy may be that serotonin selective reuptake inhibitors (but not tricyclics) act to increase levels of neurosteroids^[46]. Neuroactive steroids are synthesized from cholesterol and act directly in the brain. Some neuroactive steroids, such as allopregnanolone, produce behavioral effects that are similar to those caused by benzodiazepine drugs, including anticonvulsant and anxiolytic actions. They alter neuronal excitability by binding to allosteric sites on neurotransmitter-gated ion channels such as the GABA-mediated chloride ion channel^[47]. Allopregnanolone and progesterone (which has both neuroactive and standard steroid effects) show a significant increase across pregnancy, with the highest levels at term. Rapid withdrawal, such as that which occurs at birth, could produce a marked increase in anxiety, activation, and excitability in vulnerable women in the postpartum period^[9].

Synthetic progesterone has also been investigated for prophylactic efficacy for depression in the post-birth period^[48]. The efficacy of norethisterone enanthate was assessed in a double-blind placebo-controlled randomized clinical trial involving 180 women using non-hormonal contraception (progesterone, N=90; placebo, N=90). Women were randomly assigned to receive either a single dose of norethisterone enanthate (200 mg) or normal saline placebo by intramuscular injection within 2 days after birth. The mean depression scores were significantly higher in the progestogen-treated compared to the placebo-treated women at 6 weeks postpartum. However, no significant difference in depressive symptomatology was evident at one week or three months postpartum. This study should be considered of considerable interest due to the quality of the methodology.

3.5. Prevention studies: open-label studies:

All studies targeted the prevention of recurrence of PPD in women with at least one previous lifetime episode. No pharmacologic studies have been published on prevention of the initial episode of PPD after an index birth.

Wisner et al.^[15] conducted the first study evaluating pharmacotherapy to prevent PPD in 23 asymptomatic women with at least one previous episode of PPD according to DSM III criteria. The subjects were recruited in a 3-month prospective, open-label controlled trial. Eight women elected to receive postpartum monitoring (weekly phone contact during the first 2 weeks after birth and further phone contacts or clinic visit depending on the clinical status) and 15 women chose postpartum monitoring plus antidepressant treatment. The women were compared for recurrence (defined as an episode that fulfilled DSM-III criteria by both clinical interview and self-report evaluation). Each subject received the antidepressant to which she had responded for past episodes and the first dose was received within 24 hours after birth. Medications included fluoxetine, N=4; nortriptyline, N=7; imipramine, N=2; and clomipramine, N=2. After 3 months, the rate of recurrence was significantly lower in women taking antidepressants compared to women receiving monitoring alone (respectively 6.7% and 62.5%, $p=.0086$), and the odds for recurrence when unmedicated was 19.2 (95% CI= 1.5–1,179), independent of treatment with antidepressant during pregnancy, history of nonpostpartum depressive episodes, and breastfeeding. The major limitations of this study were the lack of randomization and double-blind design and the small sample size. Ten out of the 23 women were taking antidepressants during pregnancy and the dosage was tapered off two weeks before the delivery; therefore, the unique contribution of antidepressant taken in the study in preventing PPD recurrence remains unknown.

Sichel et al.^[49] conducted an open trial of intravenous and oral estrogen in 11 women with history of severe postpartum affective disorder. Immediately after delivery, oral estrogen was administered daily (initially 10 mg/day and tapered over 28 days to 0.625 mg/day; 2 subjects received intravenous estrogen for 2 days and then switched to oral). None of the 10 women who were compliant with treatment experienced postpartum relapse within the first postpartum year. The small sample size, lack of placebo control group and the fact that neither the subjects nor mood raters were blinded to treatment limit the results of the study, which has not been replicated.

Dalton^[50] studied 100 women with previous postnatal episodes. They received intramuscular injection of progesterone (100 mg/day for 7 days after birth) followed by progesterone suppositories (400 mg twice daily) for 2 months or until the first menstrual period after birth. The recurrence rate of PPD was reduced (10%) compared with the untreated women (68%). In a subsequent study using the same drug regimen, Dalton^[51] reported a recurrence rate of 7% among 181 women who received prophylactic progesterone. The comparison group of 21 untreated women had a recurrence rate of 67%. In both of these studies, the baseline depression severity and the criteria

for PPD recurrence were not specified. The details of the intervention were not fully described in the latter paper^[51].

3.6. Alternative pharmacological treatment for PPD:

The only alternative pharmacological agent for PPD that has been consistently studied is omega-3 polyunsaturated fatty acids (PUFAs).

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the preferred sources of omega-3 PUFAs as they are the most biologically available. It is recommended that pregnant women consume at least 300 mg of DHA daily^[52]. Thought to increase inflammatory dysregulation, low levels of DHA have been associated with increased rates of PPD in some^[53-55] but not all studies^[56-58]. For example, in one study, decreased maternal omega-3 fatty acid levels at 28 weeks gestational age are associated with increased EPDS scores at 3 months postpartum^[55]. A total of four RCTs have evaluated omega-3 PUFAs supplementation for the prevention of PPD and two RCTs for the treatment of PPD.

Omega-3-fatty acids for prevention of PPD:

Llorente *et al.*^[59] published the first RCT of 89 women who planned to exclusively breastfeed. Women were supplemented with DHA (200 mg/day) for the first 4 months postpartum. While supplemented women had higher levels of plasma DHA, there was no difference in Beck Depression Inventory (Beck) (BDI) scores at 3 weeks, 2 and 4 months postpartum. Forty-nine women underwent a diagnostic interview and seven (three placebos, four supplemented) met criteria for major depressive disorder (MDD) at some point during the 4 months. As part of an RCT of healthy pregnant women^[60], evaluating infant neurodevelopment, 119 pregnant women (mean gestational age at enrollment 16.5 weeks) were treated with placebo, DHA (220 mg) or DHA + arachidonic acid (220 mg each) from week 16 of pregnancy through 3 months postpartum. Depressive symptoms were measured at 6 weeks postpartum using the EPDS. Women were considered depressed if the EPDS score was 12 or greater. Although the study found a low incidence of PPD ($n = 7$, 5.9%), there was no difference in depression scores between the three groups. The largest trial evaluated DHA (800 mg/day) versus placebo in 2399 pregnant women recruited before 21 weeks gestational age^[61]. Women were evaluated at 6 weeks and 6 months postpartum for depressive symptoms defined as an EPDS score 12 or greater. There was no difference in depressive symptoms between groups at either time point. Most recently, in 118 women with a history of antenatal depressive symptoms, there was no difference in the prevention of PPD at 6 – 8 weeks postpartum between supplementing with EPA-rich fish oil, DHA-rich fish oil and soy oil placebo^[62, 63]. Serum EPA and DHA levels during pregnancy did not predict depression scores (BDI) postpartum. Therefore, DHA

supplementation does not appear to prevent PPD in women with or without antenatal depression. In addition, it does not seem to matter whether supplementation is started before or after the pregnancy.

Omega-3-fatty acids for treatment of PPD:

An early study that did not include a placebo group showed that omega-3 PUFAs reduced depression scores by 50% postpartum^[64]. However, in a randomized controlled follow-up trial of omega-3 supplementation in perinatal women^[65], no difference was seen between active and placebo groups. In that study, postpartum women ($n = 36$) were within 6 months postpartum and diagnosed with MDD. They had to meet DSM criteria (onset within 4 weeks postpartum) and have EPDS scores greater than or equal to 9 at enrollment. Subjects received 1.9 g/day (1.1 g of EPA and 0.8 g of DHA) in a total of four capsules per day. The placebo was corn oil. All subjects received 8 weeks of manualized supportive psychotherapy with 8 weeks of omega-3s or placebo pills. Similar to the above study, Rees *et al.*^[66] evaluated whether omega-3 PUFAs treated both antenatal and PPD, but lasted only 6 weeks. In postpartum women^[7], there was no statistically significant difference between treatment and placebo groups. Postpartum women had to have depressive episode onset within 6 months postpartum and at least a score of 13 on the EPDS, 18 on the HAM-D or 25 on the MADRS. Subjects received 6 g/day fish oil (27.3% DHA and 6.9% EPA). High omega-3 intake women were excluded.

The data to date do not support the use of omega-3 PUFAs supplementation for the treatment or prevention of PPD. It has been argued that higher doses of supplementation may have resulted in improved results^[63]; however, an earlier trial that assessed different dose ranges did not find differences between low and high doses^[64].

3.7. Internet based intervention:

Popularity and easy accessibility of computer based technologies are making internet based interventions as effective means of providing support to health care services nowadays [67] as smartphone is in everyone's hand, so access to internet is quite easy nowadays. More specifically, smartphone technology has been increasingly demonstrated as a useful tool to disseminate health information, by providing psychoeducation and/or timely interactions via short message service text messaging or two-way communication between patients and health professionals [68].

We can promote the subjective wellbeing through psychoeducation, skills training, and two-way communication with health professionals via smartphone apps in a very convenient way with the people suffering from mental illness [69]. There are meta-analysis which supports the same fact [70].

3.8. Cognitive behavior therapy:

Teratogenicity of psychotropic medications attracts the attention of clinician to psychotherapies. As cognitive distortions are present in depression, so it's a part of postpartum depression too. Moreover, antenatal depression is associated with cognitive deficits in this period too which is further responsible for development of psychopathology in her children [71].

The efficacy of CBT with tapering down of selective serotonin reuptake inhibitors (SSRIs) under integrative management for depression during pregnancy is currently under study [72].

3.9. Kangaroo mother care:

As it is well known that a bonding and attachment play an important part of infant's and mother's mental health. As there is not an established treatment for bonding disorders, then the concept of kangaroo care came in mind. Kangaroo Care is derived from its similarities to marsupial caregiving and was first suggested in Colombia in 1978. Kangaroo care is basically developed as a way of providing compensatory care for low birth weight infants and premature infants [73].

In Some studies it was found that of Kangaroo Care is effective for enhancing bonding in premature infants [74, 75]. In recent Japanese study, Matsunaga performed a two-step cluster analysis using MIBS that suggested an existence of a group of mothers with bonding disorder (14.4% n=104) characterized by severe depression as well as harsher parenting styles that were different from another group (85.6% n=619). In addition, the study showed that the optimal cut-of scores by MIBS were 3/4 at 5 days and 4/5 at 1 month, after childbirth [76].

Kangaroo Care promotes a humanizing maturation of both baby and parent alike. In British National Health Services areas psychiatric mother-and-baby units for providing Kangaroo Care have recently become quite common [77]. But the definite relationship between bonding disorder and postpartum depression is still unclear, which further needs more studies [78].

3.10. Regular exercise:

As exercises are proposed for treatment of depression as it tones parasympathetic system and increases endorphins level in brain. Many studies have been done about effectiveness of exercise in postpartum in treating depression in postpartum period too. Many recent studies support the effectiveness of the use of exercise interventions in the management of maternal depressive symptoms during the perinatal period [79, 80]. In a systematic review and meta-analysis of randomized clinical trials also found the effectiveness of exercise in reducing antenatal depression [81, 82].

In a cohort study follow up in which missing data were assessed as minimized which increases the confidence in the estimate found about supporting the effectiveness of regular exercise in treating postpartum depression. [83]

3.11. ECT:

A recent retrospective study, which evaluated catatonia among female with postpartum psychosis in a mother-baby inpatient psychiatry unit, reported the usefulness of ECT in 19 females who did not respond to lorazepam trial [84]. A retrospective study which evaluated the use of ECT in females from Turkey reported that only 3.24% of females admitted to a psychiatric inpatient unit received ECT, of which 20% of ECTs were used during the postpartum period [85]. Previous studies suggests that depression, suicidal tendency, and catatonia are the most common indications for the use of ECT in patients with postpartum psychiatric illnesses [86, 87]. Studies done on ECT in this group of patients also suggest that patients with postpartum depression and psychosis respond rapidly to ECT with an early and complete remission of symptoms [88, 89].

3.12. rTMS:

As the untreated depression has negative impact on life of pregnant mother as well as the fetus. Treatment with antidepressants is further topic of discussion as it increases the chances of various malformation, neurodevelopmental disorder and so on. We are searching for another treatment option which has no systemic side effect – rTMS gives us hope. In rTMS the energy is given to brain area non-invasively which gives patterned energy to brain. This patterned energy is responsible for adaption of neurons by changing their connection strength [90].

Kim et al found that rTMS has a medium-large effect size of 0.87 and high rates of clinical response and remission [91]. rTMS is found to be safe in most of the studies. The side effects are similar to non-pregnant population. When it's about safety, the risk-benefit ratio for antidepressant medications supports their use in some women, pregnant and lactating women are understandably reluctant to initiate pharmacotherapy due to transplacental passage and/or passage into breast milk [92]. In this scenario the rTMS has found to be offering antidepressant effect without chemical exposure to fetus which good tolerability.

When it's about acceptability survey evaluating patient acceptability to rTMS found that women were more likely to consider rTMS during pregnancy after an informational video, indicating a lack of awareness and stigma may be an obstacle in implementing rTMS as a treatment during the peripartum period [91].

References:

1. Parry BL. Postpartum psychiatric syndromes. In: Kaplan H, SB, editors. Comprehensive Textbook of

- Psychiatry. IV ed. Philadelphia: Williams & Wilkins; 1995.
2. Parry BL. Mood Disorders Linked to the Reproductive Cycle in Women. In: Bloom FE, Kupfer DJ, editors. *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press, Ltd; 1995. p. p. 1029-42.
 3. APA. *Diagnostic and statistical manual of mental disorders : DSM-5*. Washington, D.C.: American Psychiatric Association; 2013.
 4. Wisner KL, Moses-Kolko EL, Sit DK. Postpartum depression: a disorder in search of a definition. *Archives of women's mental health*. 2010; 13:37-40.
 5. WHO. *The ICD-10 classification of mental and behavioural disorders : clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization; 1992.
 6. Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA psychiatry*. 2013; 70:490-8.
 7. Josefsson A, Sydsjo G. A follow-up study of postpartum depressed women: recurrent maternal depressive symptoms and child behavior after four years. *Archives of women's mental health*. 2007; 10:141-5.
 8. Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity--adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. *Progress in brain research*. 2001; 133:1-38.
 9. 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; 157:924-30.
 10. Glynn LM, Davis EP, Sandman CA. New insights into the role of perinatal HPA-axis dysregulation in postpartum depression. *Neuropeptides*. 2013; 47:363-70.
 11. Sanjuan J, Martin-Santos R, Garcia-Esteve L, Carot JM, Guillamat R, Gutierrez-Zotes A, et al. Mood changes after delivery: role of the serotonin transporter gene. *The British journal of psychiatry : the journal of mental science*. 2008; 193:383-8.
 12. Binder EB, Newport DJ, Zach EB, Smith AK, Deveau TC, Altshuler LL, et al. A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort. *Journal of psychiatric research*. 2010; 44:640-6.
 13. Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. *Mol Psychiatry*. 2014; 19:560-7.
 14. Pinsonneault JK, Sullivan D, Sadee W, Soares CN, Hampson E, Steiner M. Association study of the estrogen receptor gene ESR1 with postpartum depression--a pilot study. *Archives of women's mental health*. 2013; 16:499-509.
 15. Wisner KL, Peindl K, Hanusa BH. Symptomatology of affective and psychotic illnesses related to childbearing. *Journal of affective disorders*. 1994; 30:77-87.
 16. Cooper PJ, Campbell EA, Day A, Kennerley H, Bond A. Non-psychotic psychiatric disorder after childbirth. A prospective study of prevalence, incidence, course and nature. *The British journal of psychiatry : the journal of mental science*. 1988; 152:799-806.
 17. Wisner KL, Peindl KS, Gigliotti T, Hanusa BH. Obsessions and compulsions in women with postpartum depression. *The Journal of clinical psychiatry*. 1999; 60:176-80.
 18. Wisner KL, Perel JM, Peindl KS, Hanusa BH, Findling RL, Rapport D. Prevention of recurrent postpartum depression: a randomized clinical trial. *The Journal of clinical psychiatry*. 2001; 62:82-6.
 19. Hay DF, Pawlby S, Waters CS, Sharp D. Antepartum and postpartum exposure to maternal depression: different effects on different adolescent outcomes. *Journal of child psychology and psychiatry, and allied disciplines*. 2008; 49:1079-88.
 20. Murray L, Cooper P. Effects of postnatal depression on infant development. *Archives of disease in childhood*. 1997; 77:99-101.
 21. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. *BMJ (Clinical research ed)*. 1997; 314:932-6.
 22. Misri S, Reebye P, Corral M, Milis L. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *The Journal of clinical psychiatry*. 2004; 65:1236-41.
 23. Wisner KL, Hanusa BH, Perel JM, Peindl KS, Piontek CM, Sit DK, et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. *Journal of clinical psychopharmacology*. 2006; 26:353-60.
 24. Yonkers KA, Lin H, Howell HB, Heath AC, Cohen LS. Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. *The Journal of clinical psychiatry*. 2008; 69:659-65.
 25. Sharp DJ, Chew-Graham C, Tylee A, Lewis G, Howard L, Anderson I, et al. A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial. *Health technology assessment (Winchester, England)*. 2010; 14:iii-iv, ix-xi, 1-153.
 26. Hantsoo L, Ward-O'Brien D, Czarkowski KA, Gueorguieva R, Price LH, Epperson CN. A randomized, placebo-controlled, double-blind trial of sertraline for

- postpartum depression. *Psychopharmacology*. 2014; 231:939-48.
27. Bloch M, Meiboom H, Lorberblatt M, Bluvstein I, Aharonov I, Schreiber S. The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study. *The Journal of clinical psychiatry*. 2012; 73:235-41.
 28. Roy A, Cole K, Goldman Z, Barris M. Fluoxetine treatment of postpartum depression. *The American journal of psychiatry*. 1993; 150:1273.
 29. Stowe ZN, Casarella J, Landry J, Nemeroff CB. Sertraline in the treatment of women with postpartum major depression. *Depression*. 1995; 3:49-55.
 30. Cohen LS, Viguera AC, Bouffard SM, Nonacs RM, Morabito C, Collins MH, et al. Venlafaxine in the treatment of postpartum depression. *The Journal of clinical psychiatry*. 2001; 62:592-6.
 31. Suri R, Burt VK, Altshuler LL, Zuckerbrow-Miller J, Fairbanks L. Fluvoxamine for postpartum depression. *The American journal of psychiatry*. 2001; 158:1739-40.
 32. Nonacs RM, Soares CN, Viguera AC, Pearson K, Poitras JR, Cohen LS. Bupropion SR for the treatment of postpartum depression: a pilot study. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2005; 8:445-9.
 33. Misri S, Abizadeh J, Albert G, Carter D, Ryan D. Restoration of functionality in postpartum depressed mothers: an open-label study with escitalopram. *Journal of clinical psychopharmacology*. 2012; 32:729-32.
 34. Amin Z, Canli T, Epperson CN. Effect of estrogen-serotonin interactions on mood and cognition. *Behavioral and cognitive neuroscience reviews*. 2005; 4:43-58.
 35. Craig MC. Should psychiatrists be prescribing oestrogen therapy to their female patients? *The British journal of psychiatry : the journal of mental science*. 2013; 202:9-13.
 36. Moses-Kolko EL, Berga SL, Kalro B, Sit DK, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. *Clinical obstetrics and gynecology*. 2009; 52:516-29.
 37. Perheentupa A, Ruokonen A, Tapanainen JS. Transdermal estradiol treatment suppresses serum gonadotropins during lactation without transfer into breast milk. *Fertility and sterility*. 2004; 82:903-7.
 38. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet (London, England)*. 1996; 347:930-3.
 39. 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; 62:332-6.
 40. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *Jama*. 2002; 287:1840-7.
 41. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. *The Journal of clinical psychiatry*. 2005; 66:148-58.
 42. Schiller CE, O'Hara MW, Rubinow DR, Johnson AK. Estradiol modulates anhedonia and behavioral despair in rats and negative affect in a subgroup of women at high risk for postpartum depression. *Physiology & behavior*. 2013; 119:137-44.
 43. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. *The British journal of psychiatry : the journal of mental science*. 1987; 150:662-73.
 44. Wisner KL, Perel JM, Peindl KS, Hanusa BH, Piontek CM, Findling RL. Prevention of postpartum depression: a pilot randomized clinical trial. *The American journal of psychiatry*. 2004; 161:1290-2.
 45. APA. American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders: American Psychiatric Publishing, Inc; 2006.
 46. Griffin LD, Mellon SH. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96:13512-7.
 47. Britton KT, Koob GF. Neuropharmacology. Premenstrual steroids? *Nature*. 1998; 392:869-70.
 48. Lawrie TA, Hofmeyr GJ, De Jager M, Berk M, Paiker J, Viljoen E. A double-blind randomised placebo controlled trial of postnatal norethisterone enanthate: the effect on postnatal depression and serum hormones. *British journal of obstetrics and gynaecology*. 1998; 105:1082-90.
 49. Sichel DA, Cohen LS, Robertson LM, Rutenber A, Rosenbaum JF. Prophylactic estrogen in recurrent postpartum affective disorder. *Biological psychiatry*. 1995; 38:814-8.
 50. Dalton K. Progesterone prophylaxis used successfully in postnatal depression. *The Practitioner* 1985. p. 507-8.
 51. Dalton K. Successful prophylactic progesterone for idiopathic postnatal depression. 1989.
 52. Greenberg JA, Bell SJ, Ausdal WV. Omega-3 Fatty Acid supplementation during pregnancy. *Reviews in obstetrics & gynecology*. 2008; 1:162-9.
 53. da Rocha CM, Kac G. High dietary ratio of omega-6 to omega-3 polyunsaturated acids during pregnancy and prevalence of post-partum depression. *Maternal & child nutrition*. 2012; 8:36-48.
 54. Shapiro GD, Fraser WD, Seguin JR. Emerging risk factors for postpartum depression: serotonin transporter genotype and omega-3 fatty acid status.

- Canadian journal of psychiatry *Revue canadienne de psychiatrie*. 2012; 57:704-12.
55. Markhus MW, Skotheim S, Graff IE, Froyland L, Braarud HC, Stormark KM, et al. Low omega-3 index in pregnancy is a possible biological risk factor for postpartum depression. *PloS one*. 2013; 8:e67617.
 56. Freeman MP. Complementary and alternative medicine for perinatal depression. *Journal of affective disorders*. 2009; 112:1-10.
 57. Wojcicki JM, Heyman MB. Maternal omega-3 fatty acid supplementation and risk for perinatal maternal depression. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*. 2011; 24:680-6.
 58. Deligiannidis KM, Freeman MP. Complementary and alternative medicine therapies for perinatal depression. *Best practice & research Clinical obstetrics & gynaecology*. 2014; 28:85-95.
 59. Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *American journal of obstetrics and gynecology*. 2003; 188:1348-53.
 60. Doornbos B, van Goor SA, Dijck-Brouwer DA, Schaafsma A, Korf J, Muskiet FA. Supplementation of a low dose of DHA or DHA+AA does not prevent peripartum depressive symptoms in a small population based sample. *Progress in neuro-psychopharmacology & biological psychiatry*. 2009; 33:49-52.
 61. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *Jama*. 2010; 304:1675-83.
 62. Mozurkewich E, Chilimigras J, Klemens C, Keeton K, Allbaugh L, Hamilton S, et al. The mothers, Omega-3 and mental health study. *BMC pregnancy and childbirth*. 2011; 11:46.
 63. Mozurkewich EL, Clinton CM, Chilimigras JL, Hamilton SE, Allbaugh LJ, Berman DR, et al. The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial. *American journal of obstetrics and gynecology*. 2013; 208:313.e1-9.
 64. Freeman MP, Hibbeln JR, Wisner KL, Brumbach BH, Watchman M, Gelenberg AJ. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta psychiatrica Scandinavica*. 2006; 113:31-5.
 65. Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *Journal of affective disorders*. 2008; 110:142-8.
 66. Rees AM, Austin MP, Parker GB. Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. *The Australian and New Zealand journal of psychiatry*. 2008; 42:199-205.
 67. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, Patel V, Haines A. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. *PLoS Med*. 2013;10(1):e1001362. doi: 10.1371/journal.pmed.1001362. <http://dx.plos.org/10.1371/journal.pmed.1001362>. [P MC free article][PubMed] [Cross Ref] [Google Scholar]
 68. Kim H, Jeong H. A nurse short message service by cellular phone in type-2 diabetic patients for six months. *J Clin Nurs*. 2007 Jun;16(6):1082-7. doi: 10.1111/j.1365-2702.2007.01698.x.][PubMed] [Cross Ref] [Google Scholar]
 69. Matthey S, Kavanagh DJ, Howie P, Barnett B, Charles M. Prevention of postnatal distress or depression: an evaluation of an intervention at preparation for parenthood classes. *J Affect Disord*. 2004 Apr;79(1-3):113-26. doi: 10.1016/S0165-0327(02)00362-2.][PubMed] [Cross Ref] [Google Scholar]
 70. Matthey S, Kavanagh DJ, Howie P, Barnett B, Charles M. Prevention of postnatal distress or depression: an evaluation of an intervention at preparation for parenthood classes. *J Affect Disord*. 2004 Apr;79(1-3):113-26. doi: 10.1016/S0165-0327(02)00362-2.][PubMed] [Cross Ref] [Google Scholar]
 71. Van den Bergh BRH, van den Heuvel MI, Lahti M, et al. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. *Neurosci Biobehav Rev*. Epub ahead of print 28 July 2017. DOI: 10.1016/j.neubiorev. 2017. 07.003.
 72. Molenaar NM, Brouwer ME, Bockting CLH, et al. Stop or go? Preventive cognitive therapy with guided tapering of antidepressants during pregnancy: study protocol of a pragmatic multicentre non-inferiority randomized controlled trial. *BMC Psychiatry* 2016; 16: 72.
 73. N. Charpak, J. G. Ruiz-Pel'aez, and Z. F. De Calume, "Current knowledge of kangaroo mother intervention," *Current Opinion in Pediatrics*, vol. 8, no. 2, pp. 108-112, 1996.
 74. J. Brett, S. Staniszewska, M. Newburn, N. Jones, and L. Taylor, "A systematic mapping review of effective interventions for communicating with, supporting and providing information to parents of preterm infants," *BMJ Open*, vol. 1, no. 1, Article ID e000023, 2011.
 75. T. Evans, K. Whittingham, M. Sanders, P. Colditz, and R. N. Boyd, "Are parenting interventions effective in improving the relationship between mothers and their preterm infants?" *Infant Behavior & Development*, vol. 37, no. 2, pp. 131-154, 2014.

76. A. Matsunaga, F. Takauma, K. Tada, and T. Kitamura, "Discrete category of mother-to-infant bonding disorder and its identification by the mother-to-infant bonding scale: a study in Japanese mothers of a 1-month-old," *Early Human Development*, vol. 111, pp. 1–5, 2017
77. A. Elkin, H. Gilburt, M. Slade et al., "A national survey of psychiatric mother and baby units in England," *Psychiatric Services*, vol. 60, no. 5, pp. 629–633, 2009.
78. M. Kokubu, A. Okano, and T. Sugiyama, "Postnatal depression, maternal bonding failure, and negative attitudes towards pregnancy: a longitudinal study of pregnant women in Japan," *Archives of Women's Mental Health*, vol. 15, no. 3, pp. 211–216, 2012.
79. Davis K, Dimidjian S. The relationship between physical activity and mood across the perinatal period: a review of naturalistic and clinical research to guide future investigation of physical activity-based interventions for perinatal depression. *Clin Psychol Sci Pract*. 2012;19(1). doi:10.1111/j.1468-2850.2012.01273.x [[Cross Ref] [Google Scholar]
80. Daley A, Jolly K, MacArthur C. The effectiveness of exercise in the management of post-natal depression: systematic review and meta-analysis. *Fam Pract*. 2009;26(2):154-162. doi:10.1093/fampra/cmn101 [[PubMed] [Cross Ref] [Google Scholar]
81. Daley AJ, Foster L, Long G, et al. The effectiveness of exercise for the prevention and treatment of antenatal depression: systematic review with meta-analysis. *BJOG*. 2015;122(1):57-62. doi:10.1111/1471-0528.12909 [[PubMed] [Cross Ref] [Google Scholar]
82. Robledo-Colonia AF, Sandoval-Restrepo N, Mosquera-Valderrama YF, Escobar-Hurtado C, Ramírez-Vélez R. Aerobic exercise training during pregnancy reduces depressive symptoms in nulliparous women: a randomised trial. *J Physiother*. 2012;58(1):9-15. doi:10.1016/S1836-9553(12)70067-X [[PubMed] [Cross Ref] [Google Scholar]
83. Songøygard KM, Stafne SN, Evensen KA, Salvesen KA, Vik T, Mørkved S. Does exercise during pregnancy prevent postnatal depression? a randomized controlled trial. *Acta Obstet Gynecol Scand*. 2012;91(1):62-67. doi:10.1111/j.1600-0412.2011.01262.x [[PubMed] [Cross Ref] [Google Scholar]
84. Nahar A, Kondapuram N, Desai G, Chandra PS. Catatonia among women with postpartum psychosis in a Mother-Baby inpatient psychiatry unit. *Gen Hosp Psychiatry*. 2017;45:40–3. [[PubMed][Google Scholar]
85. Özdemir A, Poyraz CA, Erten E, Çırakoğlu E, Tomruk N. Electroconvulsive Therapy in Women: A retrospective study from a mental health hospital in Turkey. *Psychiatr Q*. 2016;87:769–79. [[PubMed] [Google Scholar]
86. Nahar A, Kondapuram N, Desai G, Chandra PS. Catatonia among women with postpartum psychosis in a Mother-Baby inpatient psychiatry unit. *Gen Hosp Psychiatry*. 2017;45:40–3. [[PubMed][Google Scholar]
87. Babu GN, Thippeswamy H, Chandra PS. Use of electroconvulsive therapy (ECT) in postpartum psychosis—a naturalistic prospective study. *Arch Womens Ment Health*. 2013;16:247–51. [[PubMed][Google Scholar]
88. Forray A, Ostroff RB. The use of electroconvulsive therapy in postpartum affective disorders. *J ECT*. 2007;23:188–93. [[PubMed][Google Scholar]
89. Martin ME. Puerperal mental illness; a follow-up study of 75 cases. *Br Med J*. 1958;2:773–7. [PMC free article] [[PubMed][Google Scholar]
90. George, M.S., Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology* 35, 301–316. <https://doi.org/10.1038/npp.2009.87>
91. Kim, D.R., Wang, E., McGeehan, B., Snell, J., Ewing, G., Iannelli, C., O'Reardon, J.P., Sammel, M.D., Epperson, C.N., 2018. Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. *Brain Stimul*. <https://doi.org/10.1016/j.brs.2018.09.005>
92. Battle, C.L., Salisbury, A.L., Schofield, C.A., Oritz-Hernandez, S., 2013. Perinatal antidepressant use: understanding women's preferences and concerns. *J. Psychiatr. Pract*. 19, 443–453. <https://doi.org/10.1097/01.pra.0000438183.74359.46>. Perinatal