Review Article

Postpartum Depression and Role of Serum Trace Elements

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Postpartum depression (PPD) is a major depressive disorder that most often emerges within 6 to 12 weeks of delivery, but can happen any time up to 1 year after birth. In developed countries, the incidence of postnatal depression is about 10-15% in adult women depending upon the diagnostic criteria, timing of screening and screening instruments used. Mothers with depressive symptoms have been found to have more complex behavioral contacts with their children; this situation can damage family relationships, and even leads to infanticide. Various pathophysiologies are proposed for postpartum depression: Nutritional deficiencies, iron deficiency anemia, rapid decrease in the levels of reproductive hormones following delivery, alterations in hypothalamic–pituitary–adernocortical mechanism and alterations in neurotransmitter levels. Among pathophysiologies of postpartum depression, the role of trace elements is highlighted. The purpose of this review is to assess the role of trace elements including zinc, magnesium, iron and copper in PPD. Zinc as a trace element has the second highest concentration of all transition metals in the brain, and its deficiency is associated with behavioral disturbances. Lower zinc blood concentration was found in women with postpartum depression. Another trace element, magnesium, also influences the nervous system via its actions on the release and metabolism of neurotransmitters. Various studies have focused on antidepressant-like effects of magnesium and its deficiency has been reported in depression. Depletion of magnesium stores during pregnancy is hypothesized to be the cause of postpartum depression. Iron deficiency is the most common single nutrient deficiency in the world. There is an association between anemia and depressive disorders. Copper has been recognized as an essential element for many years. Iron also plays a vital role in neurological disorders and its levels are relevant to postpartum depression. Involvement of trace elements can be seen in pathophysiologies of PPD in different ways. Therefore, trace element supplementation can be an alternative treatment for patients with PPD.

Keywords: *Copper, Iron, Magnesium, Postpartum depression, Trace element, Zinc*

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Major depression is now accepted as one of the most frequent, chronic, recurrent and life-debilitating illnesses with severe morbidity and mortality, and the World Health Organization suggests that depression and heart disease will be the most ordinary diseases on Earth by 2020 (1, 2).

Depression is about twice as common in women than in men ; and women of childbearing age are at high risk for major depressive disorder (MDD) (3, 4).

Women at risk for depression experience more symptoms in menopause, the premenstrual period and the postpartum (5-7).

Postpartum depression (PPD) is diagnosed as a major depressive episode with postpartum beginning (8). Major depression can be experienced at different times of life, but PPD happens after childbirth, and therefore, it is unique. PPD involves both the mother and the child and sometimes an entire family (9). It is recognized as a major depressive disorder with postpartum onset, accompanied by depressive symptoms. According to another definition, PPD is a mild mental and behavioral disorder (10). In developed countries, the incidence of postnatal depression is about 10-15% in adult women depending on the diagnostic criteria, timing of screening and screening instruments used (11). PPD emerges most often within 6 to 12 weeks of delivery, but can happen any time up to 1 year after birth. Studies have established that depression in the postpartum time can last for months or even years after child birth (12). Clinical symptoms of PPD may recruit depressed mood, markedly reduced pleasure in almost all activities, impairment in everyday functioning, insomnia or hyper insomnia,

significant weight loss or weight gain, psychomotor agitation or retardation, loss of energy, feelings of worthlessness and excessive fault, reduced self-esteem and self-confidence, difficulty in concentration and suicidal ideation (8, 10).

Evidence proposes that maternal depression has harmful effects on new mothers, their infants, and family relationships and can influence child development (10). Mothers with depressive symptoms have been found to have more complex behavioral contacts with their children, and are less receptive and responsive and more invasive in their communications (11). This situation even leads to infanticide and furthermore can impair child's cognitive and social development (5, 13).

The reason for postpartum depression remains unclear with widespread research suggesting multi-factorial etiology. Five groups of risk factors for postpartum depression are as follows:

1. Genetic base and previous experiences: Risk of depression during postpartum is influenced by genetic susceptibility and a family history of depression has been consistently found to be a significant risk factor for PPD. Furthermore, history of previous depression, prenatal depression and maternity blue are other risk factors in this group (14, 15).
2. Hormonal changes: Sexual hormones secretions are dramatically reduced prior to menstruation or subsequent childbirth. In addition, the risk of minor and major PPD in women who experience PMS are more than other women (16, 17).
3. Alcohol use or unlawful substances (18).
4. Psychologic problems: To name some of these problems we can mention low self-esteem, poor marital relationship, childcare stress, unplanned/unwanted pregnancy and stressful life events.
5. low socioeconomic status (19, 20).

So many studies have addressed various pathophysiologies for postpartum depression. We classify these causes in several categories.

Nutritional deficiencies and/or metabolic imbalance

Nutritional status plays an important role in mental health, and poor nutrition may contribute to the pathogenesis of major depressive disorder. There is an association between MDD and deprived certain trace elements ; for example, zinc, iron and other trace elements (4). Recent studies reported notably higher depressive symptoms at postpartum among women who were anemic compared with nonanemic women (21). This part highlights the role of iron as a trace element.

Quick decline in the levels of hormones following pregnancy

Withdrawal of progesterone has been proposed as a trigger for postpartum depressive symptoms. Recently, notice has been given to the possible mood effects of neuroactive metabolites and precursors of progesterone, such as allopregnanolone (22, 23). These alterations are associated with debilitating psychiatric and neurological disorders including premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS), menstrual migraine, postpartum depression and anxiety (24).

On the other hand, levels of thyroid hormone may also change during pregnancy. Thyroid gland normally enlarges during pregnancy, but sometimes it remains enlarged or continues to enlarge after delivery, and this leads to a condition recognized as postpartum thyroid dysfunction (PPTD). Postpartum thyroid dysfunction produces transient hyperthyroidism, transient hypothyroidism, or both. Low thyroid levels can cause depressive symptoms (25).

Alterations in hypothalamic–pituitary–adernocortical (HPA axis) mechanism

HPA axis controls the adrenal cortex cortisol response to adrenocorticotropic hormone (ACTH) stimulation. Furthermore, it is secreted during stress. There is now evidence that activation of the inflammatory response system may be occupied in the pathophysiology of major depression. The postpartum period by itself is accompanied by an increased inflammatory capacity (26).

Alterations in neurotransmitter levels such as serotonin

According to recent studies, trace elements exert their antidepressant effects from neurotransmitter pathway; for example, the contribution of serotonergic system in antidepressant effect of zinc (27, 28). In another study, the involvement of nitric oxide pathway in the antidepressant effects of zinc is reported (29). On the other hand, monoaminergic and nitrergic systems are involved in antidepressant effects of magnesium (30, 31).

Despite the high prevalence of postpartum depression, up to 50% of the cases of postpartum disorders go undiagnosed or untreated (14).

Women with PPD may look for psychotherapy as a first treatment, but psychotherapy will not always be effective, and women with severe symptoms may need to consider antidepressant medications ;however, the high cost and side effects of antidepressants remain important treatment obstacles for many women (32, 33).

Furthermore, many women prefer nonpharmacological interventions due to the potential transmission of medication into breast milk and fright of addiction or dependence (34). On the other hand, negative effects of untreated PPD on short-term and long-term child development are well recognized (32).

We reviewed papers to recommend the trace elements as a supplement for treatment of postpartum depression. The purpose of this review is to draw a new view of postpartum depression treatment with lowest side effects; in fact this review is an introduction for future studies.

Zinc

Zinc as a trace element is essential for living organisms (35). To nutritionists, zinc is an essential micronutrient; to biochemists, it is a component of enzymes and other proteins ; to environmentalists, free zinc in water is a toxic pollutant; to neuroscientists, zinc is not only a micro nutrient and a component of proteins, but is also an ionic signal (36). More than 300 enzymes, including the ribonucleic polymerases, alcohol dehydrogenase, carbonic anhydrase and alkaline phosphatase, require zinc for their activities (35, 37). Zinc has the second highest concentration of all transition metals in the brain and is involved in insulin activation, metabolism of ovarian and testicular hormones, liver function, behavioral development, learning, wound healing, heavy metal poisoning protection, eye accommodation and regulation of taste sensation. It is also important in energy production, protein, carbohydrate and fat metabolism and DNA replication, transcriptions, protein synthesis, influencing cell division and differentiation, (4, 38, 39). In the central nervous system, zinc adjusts the excitatory and inhibitory amino acid neurotransmission pathways (40). Alterations of brain zinc homeostasis are related with behavioral disturbances, such as anorexia, dysphoria, impaired learning and cognitive function and with some neurological disorders namely epilepsy and alzheimer's disease (41). while not all trace elements essential for humans and animals have known functions for neural activities, trace elements such as zinc and iron are transported into the adult brain and probably are required components for neural function (42). Nutritional deficiency of Zn is common in developing countries, especially populations who consume rice-based diets (43). Several studies have shown that zinc is involved in the pathophysiology and therapy of depression (Table 1) (41). In another study, only after successful antidepressant therapy, lower blood concentration of zinc was normalized in depressed patients (44).

Magnesium

Magnesium is a trace mineral and the fourth most abundant cation in the human body (48). Mg activates about 300 enzyme systems and is involved as a coenzyme in many enzyme reactions of organisms. Mg influences the nervous system through its actions on the release and metabolism of neurotransmitters and other mechanisms. Different studies have focused on the relationships between Mg levels and a range of psychiatric illnesses, including schizophrenia and mood disorders (49, 50). Magnesium deficiency could cause abundant psychiatric symptoms including depression, behavior disturbances, headaches, generalized tonic-clonic as well as focal seizures, vertigo, tremors, irritability and psychotic behavior (51). Magnesium deficiency has been reported in depression. Magnesium is a natural calcium channel blocker and it is necessary for relaxation and appropriate nerve function. Calcium stimulates the nerves and magnesium calms them down. All these systems have been reported to be involved in the pathophysiology of depression. Magnesium also dampens the calcium ion-protein kinase C related neurotransmission and stimulates the Na-K-ATPase. (52, 53). The acute or chronic primary or secondary nervous forms of Mg deficiency remain reversible over a long period by simply normalizing the Mg intake (54). In patients with rapid cycling bipolar disorders, mood stabilizing properties of Mg supplementation have been observed (55). Based on several studies, magnesium deficiency induced depression-like behavior in mice ; and on the other hand, this ion exhibits antidepressant like activities in animal tests (46). In pregnancy, the fetus and placenta absorb huge amounts of nutrients particularly magnesium from the mother; this depletion of magnesium with not enough intake of magnesium by the mother is hypothesized to be the cause of postpartum depression. Further, lactation is known to deplete maternal magnesium as well (31).

Table 1. Summary of the effects of zinc in pathophsiology and treatment of depression

Type of Study	Zinc Concentration
Human studies:	
Depression	⇩ serum (35)
Chronic depression (women)	⇩ serum (45)
Postpartum depression	⇩ serum (46)
Animal tests/models:	
Depression + zinc treatment	⇧ brain (synaptic hippocampal zinc) (47)
Forced swim test with Zinc treatment + antidepressant treatment	⇩ immobility (44)

⇩Decrease ⇧ Increase

Iron

Iron is an essential element for humans and is distributed to different cell types in the brain in various styles. It is a component of hemoglobin, myoglobin and a number of enzymes and proteins namely oxidative enzymes and respiratory chain proteins, and is also essential for oxidative energy production. In addition, as much as 30% of the body iron is found in storage forms such as ferritin and hemosiderin in the spleen, liver and bone marrow and a small amount is associated with the blood transport protein transferrin. Iron deficiency is the most common single nutrient deficiency in the world and more than 50% of women at the reproductive age suffer from iron deficiency. It has destructive effects on mental health of these women such as deficits in cognitive function, mood, short term memory, verbal learning, attention span/concentration, intelligence. It can also lead to depression. Iron deficiency was defined as abnormal values for at least 2 of 3 tests: serum ferritin <12 µg/L, free erythrocyte protoporphyrin >1.24 mmol/L, and transferrin saturation <15%. Iron deficiency anemia was defined as iron deficiency plus anemia, with anemia defined as hemoglobin <120 g/L after modification for smoking. The RDA (Recommended Dietary Allowance) for iron of the women aged 19–50 was calculated to be 18 mg/day, based on factorial modeling considering basal and menstrual losses. The RDI (Reference Daily Intakes) is also 18 mg/day (21, 37, 56, 57). All levels of iron deficiency adversely influence tissue oxidative capacity ;and the most severe stages of iron deficiency (reduced Hb concentration) disturbs oxygen carrying capacity (58). Studies show an association between anemia and depressive disorders. Corwin and co-workers reported significantly higher depressive symptoms at postpartum day 28 among women who were anemic on postpartum day 7 compared with nonanemic women; and there was a negative correlation between hemoglobin concentrations and depressive symptoms (59). Another study showed that postpartum depression, stress and cognitive impairment in poor women may be related to iron deficiency anemia and that depression and stress respond to iron therapy. In fact, poor iron status and anemia exerted a cumulative effect over time on maternal functioning (57). Shariatpanaahi and colleagues showed that serum ferritin level was lower in depressed students than in healthy ones. This fact can also indicate the possible role of iron in brain function and the establishment of depressive mood (60).

Iron is required as cofactor for a number of enzymes involved in neurotransmitter synthesis, including tryptophan hydroxylase and tyrosine hydroxylase, as well as catabolism of these neurotransmitters. It is also required for proper myelination of the spinal cord and white matter of cerebellar folds (61). Iron acts on the molecular level and its effect on depression may be multifactorial with positive and negative effects.For example, a sufficient amount of iron is particularly needed for the synthesis of dopamine, a neurotransmitter that plays a significant role in mood disorders. We face depressed levels of blood dopamine in depression (60).

Copper

Copper has been recognized as an essential element for many years, because of its presence in important proteins and enzymes (37). It is involved in a large number of metabolic processes, including co-factor status in enzymatic activities related to brain neurotransmitter function and signal transduction. On the other hand, Cu also plays a vital role in neurological disorders. The conversion of dopamine to norepinephrine in the brain is a Cu-dependent step, with approximately eight Cu atoms loosely bound to each molecule of the enzyme dopamine β-hydroxylase (62, 63). Studies showed that copper deficiency causes a decrease in dopamine and norepinephrine concentrations in the brain of rats and it also affects many cuproenzymes, leading to defects in ATP production, lipid peroxidation, hormone activation and reproductive performance (64, 65, 66). In a survey, copper-deficient suckling rats showed a considerable decrease in body growth, a slight decrease in whole brain and cerebellar growth and a significant decrease in myelination (67). In pregnancy estrogens, by increasing hepatic ceruloplasmin synthesis, and by increasing serum copper concentrations, the noticeable elevation in maternal serum copper during the course of pregnancy is well established (43, 68). Based on these considerations, studies have been done on the relationship of Cu levels to mental depression, but findings about serum Cu levels in mental disorders show different and complex results to infer. For example, Crayton and Walsh in a study examined Cu levels in women with completed pregnancies who had a history of PPD and compared them to women who did not have depression and to women who reported having been depressed, but without a history of PPD. Cu levels were significantly higher in women having a history of PPD compared to non-depressed women and depressed women without a history of PPD (62). However, in another study, González and co-workers showed lower copper levels in depressive patients than in healthy controls (69).

Conclusion

Postpartum depression is an important threat for the mother; the child and other family members. Diverse pathophysiologies are suggested and discussed for PPD specially. The involvement of trace elements can be seen in each of the following in different ways: nutrition deficiency, iron deficiency anemia in new mothers, rapid reduction in hormone levels and alterations of neurotransmitter levels after delivery. Maybe trace elements are not the only cause of PPD, but as proposed in different pathophisiologies, they seem to be an important reason for PPD. Although half of the women involved in PPD go undiagnosed and

untreated, so many women with postpartum disorders prefer nonpharmacological treatments. Studies showed that trace elements such as zinc, magnesium, iron and copper are involved in pathophisiologies and treatment of depression. In addition, other studies demonstrated fluctuations of trace elements accompanied by alterations of hormone and neurotransmitter levels in PPD, so trace element supplementation can be an alternative for treatment of patients with postpartum depression without adverse effects of medication on breast milk and fright of addiction or dependence.

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