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IODINE DEFICIENCY AS A RISK FACTOR FOR POSTPARTUM DEPRESSIVE DISORDER IN WOMEN

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SUMMARY

Nutritional support is considered as one of the components of disease-modifying therapy for postpartum depressive disorder. Such nutrients include iodine, which is an important trace element in the development and functioning of the central nervous system. The brief review presents updated knowledge about the relationship of iodine deficiency with the development and severity of postpartum depressive disorders in women, based on the analysis and generalization of the results of domestic and international studies.

Key words: *nutrients - iodine deficiency - postpartum period - depressive disorder – women - disease-modifying therapy - nutritional support - transdermal iodine delivery*

Abbreviations: *DNA - deoxyribonucleic acid; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders IV; CNS – central nervous system; EPDS - Edinburgh Postpartum Depression Scale; PDD - postpartum depressive disorder; MPC - maximum permissible concentration; PDSS - postpartum depression screening scale; WHO - World Health Organization*

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INTRODUCTION

Postpartum depressive disorder (PDD) is a mental disorder that is a type of mood disorder that debuts at any time during the first year after childbirth and persists for at least 2 weeks, which can affect both parents (mother and father), but more often PDD develops in women (Sukiasyan et al. 2010) (Figure 1). At the same time, in clinical practice, many women are diagnosed no earlier than 6 weeks - 3 months after childbirth (WHO. Depression Fact Sheet 2020). The incidence of PDD is quite high and varies from 5% to 60.8% worldwide (Veltischev et al. 2017). On average, PDD develops in 8.9-10.1% of women in high-income countries and 17.8-19.7% of women in low- and middle-income countries (Sikström et al. 2023). PDD can be complicated

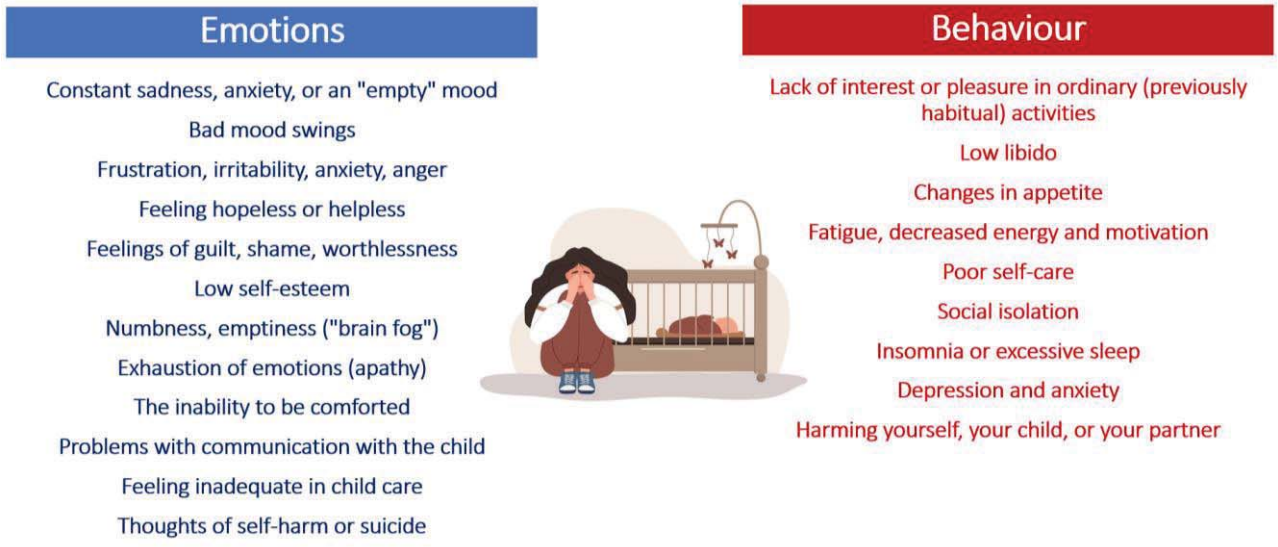

Figure 1. Emotional and behavioral disorders in women with postpartum depressive disorders

Table 1. Risk factors for postpartum depression (adapted by the authors from (USDA et al. 2024))

Unmodifiable risk factors	Modifiable risk factors
Sex (female)	Previous episodes of depressive disorders
Age (more often young – 13-19 years old, teenage mothers)	Bipolar disorder
Genetic predisposition (carriers of risk alleles of genes encoding serotonin transporters and serotonin receptors)	History of psychological stress, including stillbirth, negative attitude towards recent pregnancy, history of sexual violence
Burdened with a family history of depressive disorders, including bipolar affective disorder	Chronic disorders of the daily sleep and wakefulness cycle
	Complications during pregnancy and delivery
	Hormonal disorders, including moderate to severe premenstrual syndrome (in the anamnesis), thyroid dysfunction
	Postpartum anemia (hemoglobin level < 120 g/l)
	Postpartum hyperglycemia
	Lack of social and financial support from her husband and family
	History of drug abuse
	History of substance use
	Place of residence in large industrial cities
	Eating disorders (adherence to high-protein foods, low-tryptophan foods)
	Deficiency of nutrients (vitamins - B6, B9, B12, D; minerals - iron, zinc, selenium, iodine)

by the development of postpartum psychosis, the average prevalence of which reaches 1-2 per 1000 women after childbirth (Ekinci & Sanlier 2023), which is one of the leading causes of infant homicide (Chung 2014).

The etiology and pathogenesis of PDD are being actively studied, although an unambiguous answer about the leading mechanism of its development has not yet been found, but there are many theories about the interaction of hormones, neurotransmitters, genetics, epigenetics, nutrients, socio-environmental factors, etc. In general, PDD is considered as a multifactorial disease, in the development of which both genetic and environmental factors (for example, nutritional, physical, emotional, social) are involved (Redman 2016) (Table 1). Nutrients are not only necessary for the synthesis of neurotransmitters in the brain, but they can also indirectly affect the genomic pathways that methylate deoxyribonucleic acid (DNA). At the same time, evidence has been found of a molecular relationship between nutritional quality and psychological well-being in the postpartum period (Montero-Pedrazuela et al. 2006). Nutrient deficiency is common in women, especially during pregnancy and lactation, therefore, the increase in the number of PDD cases may be due to a deficiency of macro- and microelements, and nutritional support is considered an important and effective component of disease-modifying PDD therapy.

The aim of this brief review is to search for and summarize studies on the relationship of iodine status disorders with the development of PDD in order to update the knowledge of practicing psychiatrists about modern approaches to the diagnosis and correction of iodine deficiency as one of the components of disease-modifying therapy for this mental disorder.

SUBJECTS AND METHODS

Full-text publications in the PubMed, Web of Science, Springer, Clinical Keys, Google Schooler, E-Library databases were analyzed using keywords and combined word searches (nutrients, iodine deficiency, postpartum period, postpartum depressive disorder, women, disease-modifying therapy, nutritional support, transdermal iodine delivery) for the period from for the period from December 15, 2018 to December 15, 2023 (the search depth was 5 years). The analysis of full-text publications in English and Russian reporting on the relationship of iodine deficiency with the development and severity of PDD in women.

RESULTS

It is known that iodine mainly enters the human body from food, including seafood, egg yolks, butter, seaweed and mushrooms, which are among the best sources of iodine in the diet (USDA, FDA, and ODS-NIH Database for the Iodine Content of Common Foods Release 3.0. 2024) (Table 2). The amount of iodine in soil and water determines the iodine content in food, which leads to regional differences. Seafood and algae, especially from salt water, are a rich source of iodine. Women living in regions close to the ocean, as well as

Table 2. Recommended dietary standards for iodine (mcg/day) in female

Age	Female	Pregnancy	Lactation
From birth to 6 months	110		
7-12 months	130		
1-3 years	90		
4-8 years	90		
9-13 years	120		
14-18 years	150	220	290
Over 19 years	150	220	290

having a dietary culture with a high consumption of seafood (Coultate 2023), are more likely to have sufficient levels of iodine in their body. World Health Organization (WHO) believes that the minimum daily proportion of iodine intake per person is 0.15–0.25 mg. Most women living in Russia consume iodine three times less than this norm – 0.04–0.08 mg per day (Rospotrebnadzor.ru 2024). The need for iodine in women is especially high during breastfeeding due to increased thyroid hormone metabolism. It is known that breastfed infants receive iodine with breast milk from their mother, and the concentration of iodine in breast milk is determined by the consumption of iodine by the mother (Andersson & Braegger 2022). WHO and the United Nations Children's Fund and the International Council on Iodine Deficiency Disorders recommend slightly higher iodine intake for pregnant women - 250 mcg per day (Table 2). However, current dietary recommendations for women in the postpartum period are poorly defined, vary significantly from country to country and need to be harmonized.

Sources of iodine also include over-the-counter medications that can be taken orally or applied to the skin or mucous membrane of the vagina, contrast agents for radiography and dietary supplements. In dietary supplements, iodine is most often present in the form of potassium iodide or sodium iodide, or it contains iodine-rich seaweed. Many multivitamin/mineral supplements that women receive in the postpartum period contain iodine, often at a dose of 150 mcg. In addition, some, but not all, prenatal supplements contain iodine. Also, dietary supplements containing only iodine are available to women in the postpartum period, and many of them contain high doses, sometimes exceeding maximum permissible concentration (MPC) (NIH 2020).

The concentration of iodine in the blood of women in the postpartum period, which comes with food or dietary supplements, is correlated with the level of protein intake with food. This is very important, due to the fact that low levels of iodine and protein in the blood have an additive effect on the risk of developing and severity of PDD (Kong et al. 2023). Women in the postpartum period, especially during lactation, are particularly vulnerable to disorders associated with iodine deficiency and protein deficiency due to their increased need for iodine and protein (Pearce et al. 2016, Rodriguez-Diaz & Pearce 2020).

Cohort studies have demonstrated the effect of iodine levels during pregnancy on the development of PDD. Thus, in the framework of the Norwegian cohort study "Mother, Father and Child" with the participation of 67,812 women with 77,927 pregnancies (the average age at the time of delivery was 30.2 years), emotional stress and PDD risk were studied, which the participants reported themselves during pregnancy, and then again 6 months after childbirth (Brantsæter 2022). Iodine intake with food in the second trimester of pregnancy was assessed using a questionnaire on the frequency of iodine-containing food intake. It was shown that in 74% of women, the average level of iodine intake with food was 121 mcg/day, which was lower than the estimated average requirement of pregnant women (160 mcg/day). The frequency of identification of high levels of emotional stress in the study participants was 6.6% during pregnancy and 5.8% in the postpartum period. The incidence of PDD was high (10.3%). The authors concluded that low iodine intake (< 100-150 mcg/day) statistically significantly increases the risk of perinatal and postpartum emotional disorder and PDD. However, the use of iodine-containing dietary supplements was associated with an increased risk of perinatal emotional disorders compared to their absence. In addition, the use of such dietary supplements increased the risk of gastrointestinal disorders in pregnant women.

However, eating fish during pregnancy has a beneficial effect on the neurocognitive development of the child, while two components of fish (n-3 polyunsaturated fatty acids and iodine) are associated with this positive effect on the risk of developing PDD in mothers (Emmett et al. 2015).

Exposure to excessive iodine intake (Table 3), known as iodine contamination, can lead to thyroid dysfunction and other human health problems, including postpartum depressive disorders. Iodine contamination can come from a variety of sources, such as polluted air, water, disinfectants, food and food additives. WHO has established a standard iodine content in drinking water <300 mcg/l to exclude potential adverse effects, including for human mental health. Excessive intake of iodine with food causes the Wolf-Ciiaikoff effect, a temporary decrease in the synthesis of thyroid hormones for about 24 hours after a meal with a high iodine load (Wolff & Ciiaikoff 1948). On the one hand, the Wolf-Ciiaikoff effect is associated with the development of hypothyroidism in susceptible women (for example, patients with autoimmune thyroid disease receiving antithyroid drug therapy, or patients with increased consumption of thyroid hormones – hormone replacement therapy). On the other hand, iodine contamination can cause hyperthyroidism in women at risk, for example, with diffuse nodular goiter or latent Graves' disease (Leung & Braverman 2014).

Table 3. Maximum permissible upper levels of iodine intake (mcg/day) in female

Age	Female	Pregnancy	Lactation
From birth to 6 months	It is impossible to install		
7-12 months	It is impossible to install*		
1-3 years	200		
4-8 years	300		
9-13 years	600		
14-18 years	900	900	900
Over 19 years	1100	1100	1100

Note: *Breast milk and formula should be the only sources of iodine for infants

In connection with the above, a transdermal method of using iodine-containing drugs for the prevention and therapy of PDD is promising, since iodine intake with food above the recommended threshold may cause the development of hyperthyroidism, hypothyroidism, goiter and/or thyroid autoimmunity (Dzhikiya et al. 2018). The advantages of this nutritional support pathway for iodine deficiency conditions associated with PDD are: the ability to extend the duration of a drug with a short half-life as a result of continuous long-term iodine intake; the ability to reduce fluctuations in iodine concentration in the blood, reducing the risk of adverse effects, which is especially important for drugs with a narrow reference corridor or "therapeutic window" (according to therapeutic drug monitoring); the possibility of excluding the use of iodine-containing drugs and food additives that irritate the gastric mucosa; the ability to increase the duration of action of an iodine-containing drug without increasing the frequency of its administration, which is more effective and convenient; painless administration of iodine, which can be interrupted at any time; reducing the risk of iodine overdose and the development of serious adverse effects; facilitating the treatment of women with PDD with low motivation (with low adherence to regular intake of iodine-containing drugs with oral administration); a better safety profile of the transdermal route of iodine administration (Umarov et al. 2021).

It is known that iodine is mainly excreted by the kidneys (Zimmermann & Andersson 2012), and iodine concentration in urine is the most common indicator for assessing iodine status in children and postpartum women (World Health Organization 2024).

DISCUSSION

It is known that PDD negatively affects not only the health of the mother, but also the physical and mental health of the newborn child, which in turn has an additional negative effect on the severity of PDD, closing the "vicious circle" (Field et al. 2002). The intensity of the feeling of inability in suffering mothers with PDD can be so high that some of them perceive their lives as a "deadly swamp" (Beck et al. 2006), while mothers without PDD view the birth of their child as the "happiest stage of their lives" (Norhayati et al. 2015).

The clinical picture of PDD associated with iodine deficiency is variable (Figure 2), and cerebral symptoms may include extreme sadness, low energy levels, anxiety, episodes of unmotivated crying, mood fluctuations with a predominance of irritability, changes in the sleep and wake cycle, changes in food intake up to anorexia (Dørheim et al. 2014).

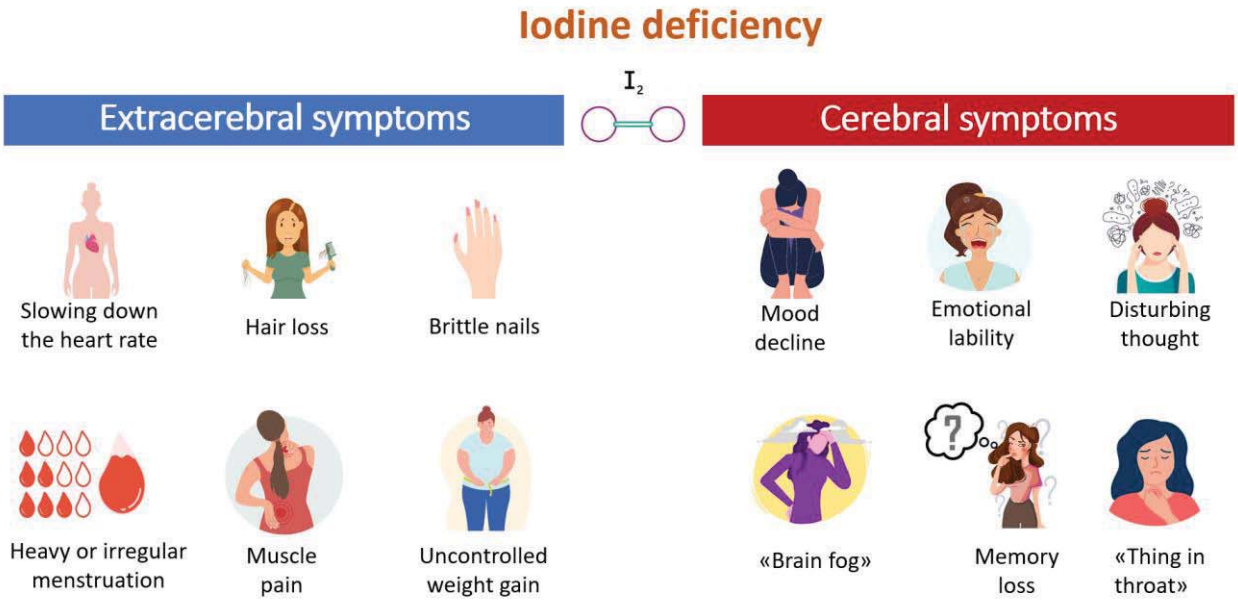

Figure 2. Cerebral and extracerebral symptoms of postpartum depressive disorder associated with iodine deficiency

A woman must have at least 4 of the following symptoms from the list in order to be able to determine that she has PDD: decreased energy; feelings of guilt or worthlessness; difficulty thinking, concentrating or making decisions; or recurring thoughts of death or suicidal ideas, plans or attempts for at least two weeks; changes in appetite or weight (more than 5% in four weeks), sleep and psychomotor activity (Payne & Maguire 2019). In addition, psychiatrists can use: postpartum depression screening scale (PDSS) as a tool for early diagnosis of the mental disorder in question (a self-report scale consisting of 35 points and assessing the presence, severity and type of symptoms of PDD); Edinburgh Postpartum Depression Scale (EPDS) (a scale of 10 points and assessing the symptoms of depression on the Likert scale); a structured clinical interview about axis 1 disorder, presented by in DSM-IV (can be used for formal diagnosis of PDD); laboratory tests of protein and micronutrient levels, including vitamins (B6, B9, B12, D) and minerals (iron, zinc, selenium, iodine).

Iodine is an important nutrient throughout a person's life, but especially during pregnancy, infancy and childhood, when thyroid hormones regulate the growth of the developing brain. Iodine plays an important catalytic and structural role, it can act as a cofactor for enzymatic reactions in the human body, including central nervous system (CNS). Iodine is one of the powerful antioxidants present in the body, and it is involved in the production of thyroid hormones (including thyroxine and triiodothyronine), which are necessary to maintain metabolism in the body, the development and functioning of the brain (Redman et al. 2016). This nutrient performs important functions in various neurobiological processes that underlie not only brain development, cognitive and intellectual functioning, but also in the development of anxiety and depressive disorders (Redman et al. 2016). PDD refers to the main consequences of iodine deficiency in women and develops in cases where iodine deficiency is pronounced and persists for a long time. In most cases of PDD, iodine deficiency in women is formed from the second trimester of pregnancy, and if iodine is supplied in sufficient quantities, then the risk of developing iodine-associated PDD is minimal. However, after the end of the second trimester of pregnancy, iodine deficiency may gradually increase and persist in the postpartum period (Trofimiuk-Mudlner & Hubalewska-Dydejczyk 2017). This is the reason for the early development of PDD, since the need for iodine intake increases during lactation (Rodriguez-Diaz & Pearce 2020). If various barriers can be overcome, such as insufficient awareness of practitioners (psychiatrists, gynecologists, internists) about the role of iodine deficiency in the development of PDD and existing economic problems in the early diagnosis of iodine-deficient mental disorders, then the benefits of nutritional support in the treatment of PDD (Choudhry & Nasrullah 2018) and methods of transdermal iodine delivery (Umarov et al. 2021).

CONCLUSIONS

Iodine deficiency is an important environmental risk factor for PDD in women, including severe depression. Monitoring and correction of iodine-deficient conditions in women during the third trimester of pregnancy and in the postpartum period is an urgent problem, since the timely appointment of disease-modifying therapy (nutritional support) for the considered mental disorder increases the effectiveness of treatment. A study of serum iodine levels and a study of urinary iodine excretion in women with PDD can be recommended to address the issue of timely and personalized administration of disease-modifying therapy, including diet therapy, dietary supplements and/or transdermal iodine delivery.

Limitations of the study

There is still a limited amount of data on the role of iodine deficiency in the development and severity of postpartum depressive disorder in women.

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Conflict of interest:

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Contribution of individual authors:

Regina Nasyrova, Natalia Shnayder & Anna Strelnik analyzed the data with advice from Olga Ismailova, Natalia Kuvshinova & Dmitry Kosterin.

Natalia Shnayder, Sagat Altynbekov, Kseniya Bikbaeva, Olga Ismailova & Natalia Kuvshinova wrote the first draft of the manuscript, which has been revised by Regina Nasyrova & Dmitry Kosterin, and upon input from the other co-authors.

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