DOI: https://doi.org/10.63769/3034-7459-2026-2-1-00-00

On the prospects for using vitamins and minerals in nutritional support of pregnancy and the prevention of recurrent miscarriage

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Abstract

BACKGROUND: The pathophysiology of recurrent miscarriage is quite complex and includes, in particular, impaired thrombus formation and elevated levels of systemic chronic inflammation. Associations between hypovitaminosis, micronutrient deficiencies, the pathophysiology of thrombophilia, and chronic inflammation suggest the potential for vitamin and mineral replenishment to reduce the risk of recurrent miscarriage (RM).
AIM: To systematize and analyze the results of clinical studies examining the relationships between various micronutrient ***status*** and RM.
METHODS: Using topological analysis of complex text data, including the ANTIFAKE system (www.antifake-news.ru), a systematic computer analysis of all available publications on the relationship between various micronutrient status and RM risk was conducted.
RESULTS: Detailed molecular mechanisms of the impact of micronutrient deficiencies on the pathophysiology of RM are described for vitamins D_3, E, B_{12}, folate, coenzyme Q10, iron, selenium, zinc, magnesium, and omega-3 polyunsaturated fatty acids. The mechanisms by which each of these micronutrients counteracts the pathophysiology of RM are unique and quite complex. For example, vitamin D_3 influences the differentiation and growth of lymphocyte populations, the expression of proinflammatory cytokines (tumor necrosis factor α, etc.), suppresses the expression of cyclooxygenase-2 and the Akt/NF-κB signaling pathway, regulates the balance of Treg/Th17 lymphocytes, and suppresses the activity of toll receptors in myometrial cells, thereby contributing to a reduction in chronic inflammation.
Evidence is provided for each of the listed micronutrients, clearly illustrating the contribution of the effects of the corresponding micronutrient deficiencies to adverse pregnancy outcomes and an increased risk of RM. The data on the use of multinutrient complexes for the prevention of RM in early pregnancy and for nutritional support of pregnancy before childbirth and during lactation are systematized.
CONCLUSION: Basic and clinical research confirms links between RM and adequate levels of vitamins D, E, B_{12}, folate, coenzyme Q10, iron, selenium, zinc, magnesium, and omega-3 fatty acids. The results of clinical studies of the use of multicomponent vitamin-mineral complexes for the prevention of recurrent miscarriage indicate prospects for reducing the risk of not only RM, but also iron deficiency anemia, preeclampsia, and low birth weight.

Keywords: miscarriage; pharmaconutrition; pharmacoinformational analysis of texts; vitamin; microelement; omega-3 polyunsaturated fatty acids; Elevit-1; Elevit-2; Elevit-3 Kormlenie.

To cite this article: Gromova O.A., Torshin I.Yu., Tetruashvili N.K. On the prospects for using vitamins and minerals in nutritional support of pregnancy and the prevention of recurrent miscarriage. Pharmacoinformatics and pharmaconutritiology. Current trends in data analysis 2026;2(1):00–00. DOI: https://doi.org/10.63769/3034-7459-2026-2-1-00-00

Background

Miscarriage (International Classification of Diseases, 10th revision, code "N96 Habitual miscarriage") is, in accordance with the criteria of the World Health Organization, a history of 3 or more consecutive spontaneous abortions before 22 weeks of pregnancy. The pathogenetic factors involved in recurrent/habitual miscarriage (RMI) are very diverse and include disorders of fertilization, implantation, differentiation of organs and tissues during fetal growth, dysfunction of T cells and other components of the immune system that prevent embryo implantation. The causes of approximately 50 % of diagnosed RMI remain unclear [1].

Clinical and epidemiological studies identified numerous factors associated with an increased risk of RMI. For example, the application of the big data of metric analysis methods to a clinically homogeneous sample of women aged 18–35 years (n = 623; 3922 indicators) allowed us to identify and to detail the complex interactions that exist between miscarriage, anamnestic and biochemical indicators, and insufficient intake of vitamins, macro- and microelements, including those contained in vitamin-mineral complexes (VMCs) [2].

Patients with miscarriage were found to have lower intakes of vitamins D_3, A, E, B vitamins, folate, potassium, magnesium, calcium, omega-3 polyunsaturated fatty acids (PUFAs), and the trace elements iron, zinc, copper, manganese, and selenium. Insufficient intake was confirmed by blood analysis of micronutrient markers. Overall, the metric analysis of the data collected in the study [2] revealed a complex relationship between PUFAs and clinical and laboratory parameters of patients, including:

- blood pressure;
- renal impairment (urine leakage, total protein, albumin, creatinine);
- hormonal status (follicle-stimulating hormone, luteinizing hormone);
- bad habits (active/passive smoking, alcohol, so-called use of "soft" drugs);
- psychological disorders (depression, suicidal tendencies, panic);
- pathologies associated with chronic inflammation (asthma, chronic bronchitis, liver pathologies, osteoarthritis);
- markers of inflammation (elevated levels of aspartate aminotransferase, alanine aminotransferase, homocysteine, ferritin, leukocytes) and blood coagulation (total number and percentage of platelets);
- lipid profile indicators;
- carbohydrate metabolism disorders (elevated levels of glucose, insulin, glycated hemoglobin);
- concentrations of toxic "heavy" metals in the blood and urine (mercury, lead, cadmium);
- micronutrient deficiencies (levels of iron, calcium, magnesium, potassium in the blood, anemia, blood levels of various forms of folates, vitamins A, B_{12}, D_3, total intake of vitamins A, B_1, B_2, PP, B_6, B_9, B_{12}, C, D, E, omega-3 PUFA, trace elements zinc, copper, magnesium, etc.).

The results of the clinical and epidemiological study [2], supported by the data from a significant array of independent clinical trials (more than 8,100 studies registered in PubMed), suggest that thrombophilia, impaired blood pressure regulation, and chronic inflammation are among the most central mechanisms of RMI pathophysiology. Increased synthesis of proinflammatory cytokines (tumor necrosis factor α (TNF-α), interferon IFNγ, interleukin IL-1β, etc.) and an increase in the proportions between proinflammatory and anti-inflammatory cytokines (e.g., the TNF-α: IL-10 ratio) are risk factors for RMI [3].

A promising approach to the long-term prevention of RMI, which can be implemented on the population scale, is compensation for combined micronutrient deficiencies – polyhypovitaminoses and polydismicroelementoses. Numerous clinical and epidemiological studies demonstrated the effects of certain vitamins on inhibiting pathophysiological processes leading to thrombophilia and increased inflammation [3]. Therefore, replenishing vitamin and mineral deficiencies is a solid pathophysiological approach to reduce the risk of not only RMI but also of many other pathologies of pregnancy including anemia, low birth weight, preeclampsia.

The relationship between the supply/intake of vitamins and microelements has been studied for a long time. In particular, the influence of electrolyte balance in pregnant with RMI was actively studied by Soviet scientists as early as the 1960s [4]. Examples of the successful use of vitamin E (tocopherol) preparations to maintain pregnancy in RMI were published in the 1940s [5] and even in the early 1930s [6]. Vitamin and microelement deficiencies on a population scale are a pressing problem in various areas of medicine (see the resource www.trace-elements.ru) .

The relevance of the problem of compensation for micronutrient deficiencies is due to the fact that large-scale clinical and epidemiological studies conducted both in Russia and abroad indicated the prevalence of micronutrient deficiencies and their relationship with numerous chronic pathologies. Thus, an analysis of a cohort of women of reproductive age (20–45 years; n = 2141) from Russia and a number of western european territories confirmed the prevalence of micronutrient deficiencies: on average, the provision of each of the 12 studied vitamins in the sample was 50 % of the sample. At the same time, less than 10 % of the participants were provided with all the studied micronutrients. Deficiency of vitamins B_6, B_9, E, magnesium, calcium was reliably associated with abnormal blood lipid profiles, an increased risk

of hyperhomocysteinemia, impaired skin barrier function, endometriosis, obesity, and immune disorders [7].

Insufficient provision of women aged 30–45 years with vitamins A, B_1, PP, B_6, B_9, B_{12}, C, K, β-carotene, calcium, iron, zinc and selenium is reliably associated with pathologies characterized by chronic inflammation: arthritis ($p = 0.0508$), bronchitis or pneumonia ($p = 0.0395$), bronchial asthma ($p = 0.0473$), increased resistance of pathogenic flora to antibiotics ($p = 0.0164$), arterial hypertension ($p = 0.0321$), myopia ($p = 0.0329$), thrombophlebitis of the veins of the lower extremities ($p = 0.0243$), chronic fatigue ($p = 0.0148$), etc. [8].

Thus, the complex relationships between insufficient vitamin and microelement status and the risk of various pregnancy pathologies, including RMI, are quite obvious.

Aim of the present work is a systematization and analysis of the results of clinical studies relationships between the availability of various micronutrients and the RMI.

Methods

Using methods of topological analysis of complex text data, including the ANTIFAKE system (www.antifake-news.ru), a systematic computer analysis of all available publications on the relationship between the availability of various micronutrients and the risk of RMI was carried out.

Search for publications

This paper presents an analysis of the results of clinical studies (PUBMED search keywords: "(habitual abortion OR recurrent pregnancy loss OR recurrent abortion OR recurrent miscarriage) AND (vitamin OR vitamins OR magnesium OR zinc OR folate OR folic OR iron OR selenium OR copper OR calcium OR pyridoxine OR cyanocobalamin OR thiamine OR riboflavin OR niacin OR myoinositol OR D-chiroinositol OR PUFA OR polyunsaturated OR biotin OR coenzyme Q10)"). The specified request to PubMed database produced 397 publications.

Analysis methodology

Using topological data analysis methods [9–11], we studied a collection of all currently available publications on micronutrients and RMI. Examples of the literature analysis methodology used in this systematic review are presented in [12, 13]. The analysis is based on identifying the most informative terms (keywords, their combinations, headings of the International Classification of Diseases 10th revision, sections of the International Nomenclature of Molecular Biology Processes "Gene Ontology" (GO), MESH headings of the PubMed/Medline database, etc.) when comparing a literature sample with a control sample. The above-described sample of publications from PubMed/Medline was used as a control sample. As a result of the systematic literature analysis, the most informative biomedical terms were identified that distinguish the texts of studies on the topic (pharmacology of micronutrients and RMI) from publications in the control. Based on the resulting list of terms, a further search and selection of sources was carried out.

The texts with a clearly manipulative nature is increased among publications on vitamins [14], a set of 397 publications was additionally checked by the ANTIFAKE system (www.antifake-news.ru). As a result, 23 publications with negative beta-score values were identified (see the description of the calculation procedure in the work [14]), i.e., publications in which manipulative content prevailed over substantive content. Typical examples of such publications were texts containing errors in the field of pharmacology (e.g., the use of single megadoses of vitamins – 200,000 IU of vitamin D, etc.), data analysis (attempts at meta-analysis of strongly heterogeneous clinical studies), and even biochemistry (erroneous views on the molecular biology of micronutrients). These studies were distinguished by numerous violations of the fundamentals of pharmacology and, due to their obviously low scientific quality, were excluded from further consideration.

Results

Here we review the results of fundamental and clinical studies examining the relationship between RMI and vitamin D, E, B_{12}, folate, coenzyme Q10, iron, selenium, zinc, magnesium, and omega-3 PUFAs. Then, the results of using multicomponent intrauterine devices (VMCs) for the prevention of RMI are discussed.

Vitamin D and miscarriage

Vitamin D influences the differentiation and growth of lymphocyte populations and the expression of proinflammatory cytokines, including that mediated by bacterial lipopolysaccharides. B-cells, T-cells, macrophages, and dendritic cells can synthesize active vitamin D and participate in processes occurring during fertilization, implantation, and maintenance of pregnancy. Insufficient levels of 25(OH)D_3 (25-hydroxyvitamin D_3) in the blood are associated with impaired embryo implantation, RMI, and preeclampsia [15].

Vitamin D reduces the expression of cyclooxygenase 2 and the inflammatory response by suppressing the Akt/NF-κB pathway, which implements the effects of the proinflammatory cytokine TNF-α [16]. The 25(OH)D_3 levels affect the transcription of RANKL and inflammatory biomarkers that are associated with the activation of peripheral blood mononuclear cells. Expression of the *CYP27B1* gene (encodes 1α-hydroxylase, the enzyme involved in the biosynthesis of the active form of vitamin D_3, calcitriol) is reduced in patients with RMI with 25(OH)D_3 levels <20 ng/ml, which is accompanied by increased expression of RANKL, TNF-α, IFN-α, ICAM and LFA-1,

and proinflammatory cytokines IL-13 and IL-4 [17]. It is important to note that decreased expression and activity of 1α-hydroxylase in the placenta is a characteristic feature of patients with recurrent RMI [18]. Decreased expression of 1α-hydroxylase in placenta is accompanied by a decreased concentration of 25(OH)D_3 and an increase in the levels of IL-17 and IL-23 [19].

Vitamin D attenuates the lipopolysaccharide-induced inflammatory response in endothelial cells by inhibiting the PI 3 K/Akt/NF-κ B signaling pathway [20]. Moreover, *vitamin D induces an anti-inflammatory response, suppresses the activity of toll receptors* in human myometrial cells (UtSM line) stimulated with lipopolysaccharides or IL-1 β.Under the influence of vitamin D_3 on cell culture, suppression of the activity of chemokines, monocyte chemoattractant protein MCP-1, chemokines CXCL-10, CXCL-11, CX 3 CL-1, proinflammatory cytokines IL-13 and TNF, toll receptors TLR-4 and TLR-5 and the triggering receptor expressed on myeloid cells (TREM) 2, and an increase in the levels of the anti-inflammatory cytokine IL-10 were shown [21].

It is important to note that vitamin D_3 (cholecalciferol) supplements help to reduce chronic inflammation levels. For example, the effect of vitamin D_3 supplements on some metabolic and inflammatory markers has been shown in patients with diabetic nephropathy and marginal vitamin D_3 status. Patients with diabetic nephropathy ($n = 50$) with marginal vitamin D_3 status received vitamin D_3 (50,000 IU/week, 3 months); lower levels of insulin ($p < 0.069$), HOMA-IR ($p < 0.001$), TNF-α ($p < 0.002$) and IL-6 ($p < 0.037$) were found after receiving supplements in the treatment group [22].

A meta-analysis of 33 studies confirmed the effect of vitamin D_3 supplementation on *biomarkers of inflammation and oxidative stress in patients with diabetes*. Vitamin D_3 supplementation significantly reduced serum high-sensitivity C-reactive protein (–0.27; 95 % confidence interval (CI) –0.35...–0.20; $p < 0.001$), malondialdehyde (–0.43; 95 % CI –0.62...–0.25; $p < 0.001$), and increased nitric oxide release (+4.33; 95 % CI 0.96–7.70), serum total antioxidant capacity (+57.34; 95 % CI 33.48–81.20; $p < 0.001$), and total glutathione levels (82.59; 95 % CI 44.37–120.81; $p < 0.001$) [23].

Vitamin D_3 deficiency *increases the number of regulatory T-lymphocytes* (Treg) in women with vitamin D deficiency and unexplained recurrent pregnancy loss. The percentage of Treg in patients with RMI ($n = 20$) was significantly lower (2.42 ± 0.27) than in the control group (3.41 ± 0.29; $p = 0.01$). Treatment of peripheral blood mononuclear cells with calcitriol significantly increased the percentage of Treg (1.23 ± 0.03) compared to baseline in the blood of patients with RMI (1.00 ± 0.03; $p = 0.01$) [24].

Vitamin D regulates the balance of Treg/Th17 lymphocytes. As it is known, in RMI, the levels of 25(OH)D_3 and the Treg/Th17 ratio is significantly reduced. After 2 months of taking vitamin D_3 supplements, a significant increase in the Treg/Th17 ratio was observed compared to that in RMI patients who did not receive vitamin D_3 supplements [25].

Vitamin D_3 plays a key role in decidualization and placental implantation, so low serum 25(OH)D_3 concentrations (<30 ng/mL) predicts the risk of preeclampsia. Pregnant women with severe vitamin D_3 deficiency (25(OH)D_3 <10 ng/mL; $n = 164$) were included in the study and randomized to receive vitamin D_3 supplementation of 400 IU/day (group 1) or 4000 IU/day (group 2). Mean maternal 25(OH)D_3 was significantly increased in group 2 from 6.4 ± 2 to 29 ± 11 ng/mL compared with group 1 (from 7.0 ± 3 to 14 ± 8 ng/mL; $p < 0.001$). Group 2 had a lower incidence of preeclampsia during the study period (8.6 % *vs* 1.2 %; $p < 0.05$). The overall incidence of intrauterine growth restriction was also lower in Group 2 (9.6 %) compared to Group 1 (22.2 %; $p = 0.027$) [26].

Vitamin E and miscarriage

The effects of vitamin E (also known as tocopherol; Greek: "bearing birth") on miscarriage have been studied for over 80 years [6]. One of the important effects of vitamin E is its antithrombotic effect. Thus, the effect of vitamin E (600 IU every 2 days) on the occurrence of venous thromboembolism (VTE) was studied in a large-scale study by Women's Health Study (WHS; $n = 26,779$). During a follow-up period of 10.2 years, VTE occurred in 482 women: 213 in the vitamin E group and 269 in the placebo group, representing a significant risk reduction of 21 % (relative risk (RR) 0.79; 95 % CI 0.66–0.94; $p = 0.010$). In women with congenital damage to genes encoding blood coagulation factors (gene variants F5 "factor Leiden", F2 "20210A", etc.), the risk of VTE was reduced by 49 % with vitamin E treatment (OR 0.51; 95 % CI 0.30–0.87; $p = 0.014$). These data indicate that vitamin E supplements can reduce the risk of VTE in women, especially with a genetic predisposition to this pathology [27].

In women with a history of spontaneous RMI ($n = 35$), statistically significant decreases ($p < 0.05$) in serum zinc, copper, and vitamin E levels and significant increases ($p < 0.05$) in serum lead and cadmium levels were found compared with controls ($n = 34$) [28]. Levels of glutathione, vitamins A, E, and β-carotene were significantly lower in women with RMI than in the control group. Conversely, plasma lipid peroxidation, alkaline phosphatase, glucose, and hemoglobin levels were significantly higher in women with RMI than in controls [29].

The effect of vitamin E and aspirin on uterine artery blood flow was shown in women with a uterine pulsatility index greater than 2.5 and a history of more than 2 miscarriages ($n = 99$). Women receiving vitamin E together with aspirin had a lower mean uterine artery pulsatility index than women receiving aspirin alone ($p < 0.001$) [30].

Folate deficiency and miscarriage

Folates, vitamins B_6, and B_{12} are essential for DNA methylation (which determines the maturation of red blood cells and lymphocytes) and for the detoxification of homocysteine. Folate and vitamin B_{12} deficiency during pregnancy and lactation is known to be a significant cause of congenital malformations, low birth weight, and the risk of developing and long-term adverse health consequences for the mother. Folate-dependent anemia, caused by impaired red blood cell formation, may predispose children to infections and chronic comorbidities [3].

In particular, folate deficiency is associated with unexplained RMI and contributes to preterm birth [31]. Polymorphisms of genes involved in folate metabolism disorders are predictors of unexplained RMI (MTHFR 677 T variant is a risk factor, MTR 2756 G variant is a protective factor, etc.) [32].

Elevated homocysteine levels and decreased serum folate levels are risk factors for early RMI (n = 123). Elevated fasting homocysteine levels greater than 18.3 μmol/L were a risk factor for early RMI (OR 3.6; 95 % CI 1.2–12.7). Serum folate concentrations less than 8.4 nmol/L were also associated with the risk of RMI (odds ratio (OR) 2.1; 95 % CI 0.9–4.8) [33]. A meta-analysis confirmed that folate deficiency-associated fasting hyperhomocysteinemia was associated with a 3-fold increased risk of recurrent early pregnancy loss (OR 2.7; 95 % CI 1.4–5.2) [34]. Another meta-analysis of 8 studies showed that hyperhomocysteinemia was associated with an increased risk of placental abruption (OR 5.3; 95 % CI 1.8–15.9) and spontaneous abortion [35].

Folate supplementation and its synergist pyridoxine as part of combination pharmacotherapy contribute to the effective prevention of RMI in patients with a predisposition to thrombophilia. In a study of 351 patients with RMI, only 29 (8 %) had no significant blood coagulation disorders. Of the remaining 322 patients, 12 % had blood coagulation disorders (platelet dysfunction, factor XIII deficiency, protein S deficiency, genetic variant of factor V, antithrombin deficiency, heparin cofactor II deficiency, protein C deficiency). Antiphospholipid syndrome was diagnosed in 195 patients (60 %), and sticky platelet syndrome was detected in 64 (20 %). All patients underwent therapy with acetylsalicylic acid, low molecular weight heparin, folic acid 1 mg/day + pyridoxine 50 mg/day. As a result of this therapy, only two patients experienced a miscarriage; all others had normal pregnancies and deliveries. There were no pregnancy-related thromboses, complications during childbirth, or episodes of postpartum thrombosis [36].

Vitamin B_{12} and miscarriage

Low vitamin B_{12} levels are a risk factor for very early RMI. A study of women with low serum B_{12} levels (n = 100) showed that 87.5 % had a history of RMI [37]. Vitamin B_{12} levels were significantly reduced in patients with RMI compared with the control group (mean concentrations 197 pg/mL *vs* 300 pg/mL; p = 0.004). The lowest vitamin B_{12} levels in the blood serum (172 pg/ml) was observed in patients with primary termination of pregnancy [38].

In a group of patients with RMI (n = 30), correlations between homocysteine, folate, and vitamin B_{12} concentrations were studied.The mean serum vitamin B_{12} concentration was 178.3 pg/ml and was lower than in the control group (268.6 pg/ml; p <0.001). A strong negative correlation (R = –0.5397; p <0.01) was found between folate levels and homocysteine concentrations in the group of women with RMI and a very high negative correlation (r = –0.9586; p <0.001) in the control group. As the number of miscarriages increased, mean homocysteine concentrations increased and mean folate concentrations decreased [39].

Effects of other vitamins

Alpha-lipoic acid reduces endometrial inflammasome expression in women with recurrent pregnancy loss. Supplementation with alpha-lipoic acid (600 mg) and vitamin E (400 IU) significantly reduced IL-6 concentrations in hemodialysis patients (n = 85) [40].

Peripheral blood mononuclear cells from women with idiopathic recurrent pregnancy loss treated with **coenzyme Q10** showed a significantly lower percentage of Th1 cells (p <0.005) in pregnant women with a history of RMI than in untreated women. Furthermore, IFN-γ and TNF-α levels were significantly reduced [41].

A meta-analysis of 9 randomized controlled trials (n = 509) confirmed that coenzyme Q10 supplementation (60–500 mg/day for 8–12 weeks) can reduce TNF-α and IL-6 levels in chronic inflammatory diseases. Oral coenzyme Q10 administration resulted in a significant reduction in TNF-α (–0.44 mg/dL; 95 % CI –0.81...–0.07) and IL-6 (–0.37; 95 % CI –0.65...–0.09; p = 0.01) levels. Subgroup analysis showed a significant reduction in TNF-α and IL-6 levels in patients with a body mass index <26 kg/m^2 [42].

Iron and miscarriage

Serum ferritin levels are inversely associated with the rate of miscarriage in women with recurrent miscarriage. A study of women with RMI (n = 84) and women of reproductive age without known fertility problems (n = 150) found that women with RMI had lower s-ferritin levels (39.9 μg/L) than controls (62.2 μg/L), which was accompanied by a higher prevalence of low iron stores (s-ferritin <30 μg/L, 35.7 % in RMI compared with only 13.7 % in controls). Therefore, women with low s-ferritin levels may benefit from iron supplementation [43].

Iron supplementation is also beneficial in exacerbation of heart failure associated with reduced protein intake, fluid

retention, inflammation, and the use of antiplatelet agents. For example, a proteomic study of 2,357 patients with exacerbation of heart failure showed that independent predictors of iron deficiency (transferrin saturation <20 %) were female gender, lower protein intake, higher heart rate, the presence of peripheral edema and orthopnea, chronic kidney disease, lower hemoglobin levels, higher C-reactive protein levels, and lower serum albumin levels [44].

Selenium and miscarriage

A decrease in the average selenium content in hair was found in the group of patients with RMI (0.14 μg/g) compared to the control group (0.34 μg/g) [45]. The average selenium levels in erythrocytes in patients with RMI were 119.55 ± 32.94 (55–170) ng/ml, which was significantly lower compared to the control group (150.85 ± 37.63 (87–225) ng/ml; p <0.01) [46].

Zinc and miscarriage

Zinc stimulates the function and growth of T-lymphocytes and is one of the most important micronutrients for supporting innate and acquired antiviral immunity [3]. In a study of middle-aged patients (n = 1055), an inverse relationship was found between serum zinc levels and inflammatory markers in women: IL-6 (p = 0.0236), TNF-α (p = 0.0017), C-reactive protein (p = 0.0301) [47]. Zinc helps reduce inflammation and remove heavy toxic metals in patients with a history of spontaneous RMI. As noted above, RMI is accompanied by decreased serum zinc, copper, and vitamin E levels [28].

Magnesium and miscarriage

Magnesium deficiency promotes the development of proinflammatory reactions and sugar metabolism disorders, which affects the risk of RMI [48]. For example, both insufficient magnesium intake (<250 mg/day) and serum magnesium concentrations (<0.75 mmol/L) were associated with elevated serum C-reactive protein concentrations [49]. Adequate magnesium intake from food and medications reduces the risk of type 2 diabetes by improving insulin resistance and reducing inflammation. Non-diabetic patients aged 40–79 years were prospectively followed for an average of 15.6 years (n = 1999); 417 patients developed type 2 diabetes. The incidence of type 2 diabetes was significantly reduced with increasing quartile of magnesium intake (≥148.5, 148.6–171.5, 171.6–195.5, and ≥195.6 mg/day; p for trend = 0.01). In stratified analyses, statistically significant interactions were observed between magnesium intake and homeostasis levels modeled for insulin resistance, high-sensitivity C-reactive protein, or alcohol consumption on the risk of type 2 diabetes (all p <0.05) [50].

Omega-3 polyunsaturated fatty acids and miscarriage

Free saturated fatty acid levels were significantly higher in patients with RMI (16.8 ± 6.7 mg/100 ml) than in the control group (8.6 ± 3.7 mg/100 ml; p <0.01) [51]. A lower ratio of omega-3 PUFAs docosahexaenoic acid to arachidonic acid was associated with higher serum IL-8 levels, poor sleep quality, and abnormally shortened gestational age [52]. Higher dietary omega-3 PUFA intake was associated with a lower risk of recurrent VTE. In a study of 595 patients, 98 recurrent VTE and 227 deaths were observed during the follow-up period. Inverse correlations were found between higher omega-3 PUFA intake and the risk of VTE (OR 0.45; 95 % CI 0.20–1.01) and deep vein thrombosis (OR 0.49; 95 % CI 0.24–0.97) [53].

Antiviral immunity

Pregnancy is often characterized by a weakening of the female immune system and increases the risk of RMI, which indicates the need for special measures to strengthen the immune system. Data from basic and clinical research suggest that micronutrient deficiencies negatively affect the functioning of acquired immune systems and, consequently, the effectiveness and safety of vaccination, including against various RNA-viruses (influenza viruses, measles, RS virus, coronaviruses, etc.). For example, supplementation with vitamins A and D during immunization with an influenza virus vaccine improved the weak antibody response in the mucosa of vitamin-deficient mice [54]. Supplementation of mice with vitamins during vaccination against pneumococcus increased immunogenicity and survival after infection with *Streptococcus pneumoniae* [55].

An analysis of the molecular biology of the SARS-CoV-2 coronavirus has shown that increasing the body's supply of vitamins A, D_3, magnesium, and zinc is an important, but underutilized, resource for enhancing the activity of innate immune systems against coronaviruses and other RNA viruses (primarily the interferon system). At the same time, existing data indicate that these and other micronutrients, as well as a number of pharmaceuticals, may exhibit direct antiviral activity by inhibiting viral replication in cell cultures [56].

Multicomponent vitamin-mineral complexes and miscarriage

Adherence to simplistic views and the emphasis on "the most important" micronutrients (folate, iodine, iron, vitamin A) significantly reduces the effectiveness of preventing pregnancy pathologies and congenital malformations. Evidence shows that the use of multicomponent VMCs with folic acid throughout pregnancy is more effective in reducing the risk of pregnancy and fetal pathologies than

taking folic acid or other micronutrients alone [57]. Here are several arguments for the preferential use of multicomponent VMCs during pregnancy to prevent RMI.

Firstly, the use of multicomponent VMCs in patients with RMI is justified due to the *presence of polyhypovitaminosis in such patients*. For example, a study of roles and microelements, minerals, and vitamins in women with RMI (n = 39) showed that RMI were more often characterized by low levels of cholecalciferol, phylloquinone, microelements selenium, zinc, copper, magnesium, and potassium, reduced antioxidant status of the blood, and an increased calcium/magnesium ratio in the blood [58]. In a study of a clinically homogeneous sample of women aged 18–35 years (n = 623; 3922 indicators), associations were established between RMI and lower intake of vitamins D, A, E, B vitamins and folates, potassium, magnesium, calcium, omega-3 PUFAs, and microelements iron, zinc, copper, manganese, and selenium [2].

Secondly, multivitamin supplements help reduce the risk of pregnancy loss due to *placental abruption/ preeclampsia*. For example, a meta-analysis of 17 studies showed that women who received VMCs had a lower risk of developing preeclampsia (OR 0.68; 95 % CI 0.54–0.85), while the chances of developing multiple pregnancies, on the contrary, were higher (OR 1.38; 95 % CI 1.12–1.70) [59].

Third, supplementation of men from couples with a history of miscarriage with certain vitamins and microelements also *helps prevent RMI*. For example, supplementation with vitamin E and zinc improves sperm chromatin parameters and reduces sperm DNA fragmentation in couples with RMI [60]. Vitamin C influences the expression profile of genes encoding protamine proteins in sperm of male partners in couples with RMI. Significant differences were found in sperm morphology, protamine deficiency, and apoptosis between the two groups before and after vitamin C supplementation [61].

Fourth, VMCs promote *normalization of the proinflammatory cytokine profile*, thereby reducing chronic systemic inflammation. Ten-week intake of omega-3 PUFA, vitamin D_3, and B-group vitamins normalized elevated intracellular cytokine levels in patients with reproductive failure (n = 150). The TNF-α to IL-10 ratio decreased from 71.6 to 21.0 (p <0.0001), and the IFN-γ: IL-10 ratio decreased from 24.5 to 12.5 (p <0.0001). The improved ratios were achieved primarily due to increased IL-10 expression (p = 0.0007), but also due to a moderate decrease in stimulated TNF-α expression (p = 0.008) [3].

Let us also provide other examples of the effectiveness of VMCs for the prevention of RMI. Triple therapy with aspirin, prednisone, and multivitamins was shown to be effective in treating *unexplained cases of RMI* (n = 106) compared to folic acid monotherapy (n = 65). Treatment effectiveness was assessed as an indicator of successful treatment (12-week pregnancy with an obvious embryo and fetal heart, occipital bone thickness <0.25 cm, size corresponding to gestational age, absence of early malformations). Although the rate of successful pregnancies was the same with multivitamin therapy (89.6 %) and in the control group (92.3 %; p = 0.343), the rate of successful treatment was higher with multivitamin therapy (86.3 %, in the control group – 53.3 %; p <0.001) [62].

The efficacy of combination therapy for RMI with aspirin, prednisone, and the Elevit VMC was demonstrated in a study including 155 patients with unexplained recurrent early pregnancy loss: 89 patients (57.42 %) received aspirin, prednisone, and Elevit, and 66 patients (42.58 %) in the control group took folic acid alone. The thickness of the fetal hyaline layer, heart, and cervix were examined by ultrasound after 12 weeks. Visible fetal embryos, fetal heart, and nuchal bone thickness <0.3 cm were used as indicators of successful treatment. 67 patients in the experimental group (success rate was 83.75 % (67/80)) and 33 patients in the control group (success rate was 54.10 % (33/61)) were successfully treated. Thus, the effect of triple therapy with aspirin, prednisone and Elevit in patients with unexplained recurrent early pregnancy loss is significant [63].

Among the various multi-micronutrient intrauterine contraceptives for pregnant women, Elevit Pronatal (Bayer, Germany) stands out as the most comprehensively supported by evidence. Data on the efficacy and safety of this intrauterine contraceptive for the prevention of congenital malformations and pathophysiological conditions associated with RMI during pregnancy have been obtained.

Micronutrient deficiencies during pregnancy are associated with obvious congenital malformations (digital fusion and other limb defects, teething disorders, hernias, etc.) and congenital malformations that manifest themselves in early childhood (congenital heart defects, defects of the ureter, gallbladder, etc.). Zinc, for example, regulates the activity of more than 1,200 zinc-dependent proteins, vitamin A, and vitamin PP play an equally important role in the prevention of defects in teething and the development of fingers, ears, lungs, diaphragm, and gallbladder. Deficiencies of zinc, vitamins A, E, D, C, and any of the B vitamins (including folates, pyridoxine, and cyanocobalamin) stimulate the formation of both "minor" and "major" malformations. All these micronutrients are included in Elevit Pronatal [64].

The use of Elevit Pronatal in patients with hyperandrogenism significantly reduced the incidence of pregnancy complications such as gestosis and premature detachment of a normally located placenta. No congenital malformations were detected in the newborns of any patient receiving Elevit Pronatal, and the incidence of threatened miscarriage was significantly higher in pregnant women who

did not take Elevit Pronatal. The high clinical efficacy of Elevit Pronatal in its prophylactic use is also demonstrated by a significantly reduced incidence of iron deficiency anemia in pregnant women [65].

A study of women with RMI (n = 220), conducted at the D.O. Ott Research Institute of Obstetrics, Gynecology and Reproduction (St. Petersburg), showed that taking Elevit Pronatal 3 months before the expected pregnancy leads to the normalization of homocysteine levels in women with RMI, thereby effectively counteracting the pathophysiology of RMI [66].

Large-scale clinical-epidemiological randomized and cohort controlled studies conducted in Hungary have shown that the use of the multivitamin preparation Elevit Pronatal in the periconceptional period significantly reduces the prevalence of birth defects in the study populations compared to folic acid monopreparations. Thus, a comparison of data from a large-scale (n = 5000) randomized study conducted in Hungary, using multivitamins containing 0.8 mg/day of folic acid, and long-term data from the Hungarian congenital anomalies surveillance service allowed us to draw an important conclusion: the Elevit Pronatal VMC, containing 0.8 mg/day of folic acid, is more effective in preventing neural tube defects and heart defects than high doses of folic acid monopreparations [67].

Overall, the Elevit-1/-2/-3 VMC line (Table 1) is focused on a differentiated approach to nutritional support for women at different stages of pregnancy and breastfeeding. For example, Elevit-1 and Elevit-2 VMCs contain the active form of folate, metafolin, which is characterized by a higher absorption rate than folic acid. Since no metabolic conversion is required to form this biologically active vitamin B9, it is effective in replenishing folate deficiency in pregnant women with genetic defects in methylenetetrahydrofolate reductase and with elevated homocysteine levels in the blood. Vitamin A in Elevit-1 is important for placental development, gonadotropin production, placental lactogen, and immunoglobulins. The combination of vitamins C, D_3, and zinc is necessary for supporting cellular and humoral immunity.

Table 1. *Micronutrient composition of vitamin-mineral complexes Elevit-1, Elevit-2 and Elevit-3 Kormlenie*

Micronutrients	Elevit-1, 1 tablet	Daily requirement, 1st half of pregnancy, %	Elevit-2, 1 tablet	Daily requirement, 2nd half of pregnancy, %	Elevit-3, 1 tablet	Daily requirement for nursing mothers, %
Docosahexaenoic acid (omega-3), mg	–	–	200	29	200	29
Eicosapentaenoic acid (omega-3), mg	–	–	80	13	–	–
Vitamin A, μg (retinol equivalent)	770	86	771	77	721	55
Vitamin B1, mg	1.4	93	1.4	82	1.4	78
Vitamin B_2, mg	1.4	78	1.4	70	1.6	76
Vitamin B_5, mg	6	120	6	100	7	100
Vitamin B_6, mg	1.9	95	1.9	83	2	80
Vitamin B_{12}, μg	2.6	87	2.6	74	2	57
Vitamin C, mg	85	94	85	85	60	50
Vitamin D, μg	5	50	5	40	5	40
Vitamin E, mg TE (tocopherol equivalent)	10	67	10	59	5	26
Niacin, mg	18	90	18	82	17	74
Active folate metafolin® (calcium L-methylfolate), μg	451	–	225	33	–	–
Terms of folic acid, μg	400	100	200	33	–	–
Folic acid, μg	–	–	200	33	200	40
Biotin, μg	30	60	30	60	35	70
Calcium, mg	125	13	–	–	120	9

End of table 1

Micronutrients	Elevit-1, 1 tablet	Daily requirement, 1st half of pregnancy, %	Elevit-2, 1 tablet	Daily requirement, 2nd half of pregnancy %	Elevit-3, 1 tablet	Daily requirement for nursing mothers, %
Magnesium, mg	100	25	57	88	–	–
Iron, mg	14	78	29	91	9	50
Copper, mg	1	100	1	68	–	–
Iodine, μg	150	100	150	67	150	52
Zinc, mg	11	92	10	92	9.5	63
Manganese, mg	2	100	–	–	–	–
Selenium, μg	60	109	60		35	54
Lutein, μg	–	–	–	–	250	5

Elevit-2 is prescribed in the second trimester and contains two types of omega-3 PUFAs – eicosapentaenoic acid and docosahexaenoic acid – which are essential for the fine regulation of inflammation and the development of all types of fetal cells, including visual analyzer cells, neurons, and cardiomyocytes. Vitamin A is essential for the development of the fetus's lungs, as it ensures the synthesis of surfactant, which stabilizes the alveoli and ensures lung expansion during the first breath, as well as for the development of a fetus with normal anthropometric parameters.

In particular, a meta-analysis of 9 randomized controlled trials ($n = 5710$) showed that docosahexaenoic acid supplements (450–800 mg/day) were associated with significantly higher birth weight (+101.7; 95 % CI 57.36–146.06; $p = 0.00001$) and fewer cases of low birth weight (OR 0.53; 95 % CI 0.33–0.86; $p = 0.01$) [68].

Elevit-3 Kormlenie contains vitamins and minerals, including docosahexaenoic acid, iodine, and vitamin A, helping to enrich breast milk with essential micronutrients, supporting the baby after birth and healthy brain and vision development. Docosahexaenoic acid also effectively helps prevent postpartum depression and promotes long-term intellectual development in newborns.

A meta-analysis of 9 studies showed that docosahexaenoic acid supplementation was associated with a higher psychomotor development index than the placebo group (+1.47; 95 % CI 0.23–2.72; $p = 0.02$). Subgroup analysis demonstrated that docosahexaenoic acid supplementation was associated with better scores on language skills scales (+2.05 points; 95 % CI –0.16... 4.26; trend $p = 0.07$) [69].

Conclusion

The pathophysiology of RMI is complex and includes, in particular, the impaired thromboembolism and the elevated levels of systemic chronic inflammation. Associations between hypovitaminosis, microelement deficiencies, the pathophysiology of thrombophilia, and chronic inflammation suggest the potential for vitamin and mineral replenishment to reduce the risk of RMI. This paper presents the results of fundamental and clinical studies examining the relationships between RMI and the availability of vitamins D, E, B_{12}, folates, coenzyme Q10, iron, selenium, zinc, magnesium, and omega-3 PUFAs. It also presents the results of using multicomponent intrauterine complexes (VMCs) to prevent RMI recurrences, malformations, preeclampsia, and low birth weight. The potential for using the micronutrient complexes Elevit-1, Elevit-2, and Elevit-3 Kormlenie for nutritional support of pregnant and lactating women is described.

Additional information

Funding source. The authors declare that there was no external funding for the preparation of this publication.

Disclosure of interests. The authors declares that there was no external funding for the preparation of this publication.

Authors' contribution. All authors confirm that they meet the international ICMJE criteria for authorship (all authors have made a significant contribution to the development of the concept, preparation of the article, and have read and approved the final version before publication). All authors contributed equally to the writing of the article.

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Submitted: 15.03.2026. **Accepted:** 22.04.2026. **Published online:** 00.00.0000.

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