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FEATURES OF THE GESTATION PERIOD AND BIRTH OUTCOMES UNDER VITAMIN D DEFICIENCY (LITERATURE REVIEW)

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ABSTRACT

For the past decade there were researches showing that vitamin D deficiency during pregnancy causes large spectra of obstetric complications, unfavorable perinatal and neonatal outcomes that include the development of preeclampsia, inevitable miscarriage, preterm birth, gestational diabetes, adiposis, bacterial vaginosis, intrauterine growth retardation, defect of embryonic skeletal formation, and decrease of body bone mass

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Vitamin D is related to a group of fat-soluble vitamins and is determined by the level of serum 25-hydroxy vitamin D concentration (25[OH]D). In limited amount it comes into a human body with foods, supplements, and is synthetized in the sun exposure due to ultraviolet rays if enough skin surfaces are not covered with clothes.

As of today, low level of vitamin D during pregnancy, related to especially vulnerable category of patients, is a topical healthcare issue in many countries of the world [1-3]. It was revealed that vitamin D deficiency during pregnancy can cause unfavorable effect during the gestation course, delivery, and perinatal outcomes. In Kazakhstan, the determination of serum vitamin D level and its correction is not included into the list of main and additional diagnostic and treatment activities of clinical gestation protocols. This situation requires proper attention and review.

At the present time the most researchers consider serum 25[OH]D level more than 50 nmol/L [4, 5] as normal, insufficient - 25[OH]D concentration level 37.5-80 nmol/L, deficiency - less than 37.5 nmol/L [6].

According to the recommendations of the Institute of Medicine [5], serum 25 (OH) D concentration of 50-125 nmol/L is considered as sufficient level, concentration 25[OH]D < 30.0 nmol/L (< 12 ng/mL) shows the risk of vitamin D deficiency, and level of 30.0-49.9 nmol/L (12-20 ng/mL) shows its insufficiency.

However, Hasslöf P. et al. classify the level 25[OH]D < 50 nmol/L as insufficiency, and deficit is its concentration in the amount 25[OH]D < 25 nmol/L [7].

Low level of vitamin D can be caused by its insufficient income with foods, inhibiting of its synthesis in skin, and due to additional factors that influence on absorption and metabolism of vitamin D [8, 9].

Note that low blood level of vitamin D is a wide spread problem among pregnant women, especially vegetarians, and those who spent little time in the sun, and up to 30% among western women [5, 8, 10-16].

The research results on vitamin D concentration in maternal blood and in cord blood of a newborn in extremely different seasons showed the increase of its concentration in summer period in comparison with winter period (mean 22.2 ± 6.5 ng/ml versus 16.5 ± 8.2 ng/ml ($p < 0.001$) respectively for the mothers, and 31.3 ± 9.4 ng/ml versus 22.7 ± 11.0 ng/ml ($p < 0.0001$) for the newborns, respectively) [17].

The most prominent seasonal variations with the lowest serum vitamin D concentrations are noted in winter period, January month [7].

Other researches showed geospatial distribution of vitamin D insufficiency among women living in different continents and world countries, and that is reliably true in winter period and north polar regions with its distribution from the north to the south. The average 25[OH]D serum concentration for pregnant women was 52.1 nmol/L in winter, and 68.6 nmol/L in summer ($p < 0.001$) [7, 18].

For the past decade there were researches showing that vitamin D deficiency during pregnancy causes large spectra of obstetric complications, unfavorable perinatal and neonatal outcomes that include the development of preeclampsia, inevitable miscarriage, preterm birth, gestational diabetes, adiposis, bacterial vaginosis, intrauterine growth retardation, defect of embryonic skeletal formation, and decrease of body bone mass [19, 20].

Cochrane database of systematic reviews of clinically significant researches contains the analysis of research results regarding 25[OH]D influence on gestation and birth outcome. The results of these observations show that insufficient serum 25[OH]D level is caused by gestational diabetes development (pooled odds ratio (OR) 1.49, 95% confidence interval (CI) 1.18 to 1.89), preeclampsia (1.79, 1.25 to 2.58), and small fetal weight for gestational age (1.85, 1.52 to 2.26) [11].

Data of systematic review of other authors [21] also show the development of high risk of preeclampsia (OR 2.09 (95% CI 1.50–2.90)), gestational diabetes (OR 1.38 (1.12-1.70)), preterm birth OR 1.58 (1.08–2.31), and small fetal weight for gestational age (OR 1.52 (1.08-2.15)) for women patients with 25[OH]D concentration less than 50 nmol/L.

The role of vitamin D connection with excess body mass and adiposis during the gestation period is confirmed [6].

There is data showing the interconnection of vitamin D deficiency with the development of bacterial vaginosis during pregnancy. Bacterial vaginosis is a widespread recurrent vaginal infection among women of reproductive age that occurs most frequently during the first trimester of pregnancy [22].

The results of investigations by Hasslöf P. et al. show that bacterial vaginosis is more frequent among pregnant women with vitamin D

insufficiency than among healthy women of control group (26% versus 5% ($p < 0.01$)) [7].

Other researchers have also confirmed the high risk of infection under low vitamin D concentration that can cause preterm birth [23-28].

The recently conducted meta-analysis of 10 098 patients showed the interrelation between the low vitamin D level (< 20 ng/mL) and increased risk of preterm birth development (OR = 1.29, 95% CI: 1.16, 1.45) [29].

In addition, vitamin D deficiency from early pregnancy causes the increase of operative deliveries.

Merewood A. et al. [30] have analyzed the relation between 25[OH]D level in maternal serum and primary delivery by cesarean operation. It was revealed that in case 25[OH]D serum concentration less than 37.5 nmol/L had 28% of cesarean operations, whereas 25[OH]D 37.5 nmol/L or more was in 14% of cesarean operations ($P = 0.012$).

Another group of scientists also proves the increase of cesarean operation risk by two times under vitamin D deficiency [5].

The meta-analysis of recent 15 scientific researches has revealed the significant interrelation between vitamin D deficiency, its prescription as mono-therapy or in combination with calcium and risk of pregnancy complications development. Pregnant women (n=219) who took vitamin D had lower risk of preeclampsia development in comparison with those who did not take vitamin D or took placebo.

The positive influence of vitamin D intake was also observed in decrease of risk of gestation diabetes and preterm birth development. The research results for 493 patients showed that the weight of newborns of those women who took vitamin D during pregnancy was not less than 2500 g in comparison to those who did not have therapy or took placebo.

Thus, the meta-analysis results showed the significance of 25[OH]D deficiency and efficiency of vitamin D prescription to decrease the risk of unfavorable outcomes during the gestation period [31].

The up to date published results of randomized double-blind and placebo-controlled study conducted for 90 pregnant women having at least one risk factor of gestation diabetes development, among which 46 patients took 5000 ME of vitamin D on daily basis up to 26 weeks of pregnancy, and 44 patients took placebo, revealed that development of gestation diabetes is statistically higher for those who took placebo than for the main group (35.9% versus 10.9%, $p < 0.005$). The obtained results show the reasonability to prescribe vitamin D to prevent gestation diabetes during pregnancy [32].

Under the prospective double-blind randomized placebo-controlled study, 60 women with high risk of preeclampsia development in the period of 20-32 weeks of pregnancy were prescribed to take 50000 ME of vitamin D3 every two weeks, and 1000 mg of calcium carbonate (n = 30) per day, among them 30 patients took placebo. As a result, the pregnant women who took combined cholecalciferol and calcium supplement, comparing to those who took placebo, had lower level of fasting plasma glucose, serum insulin, and insulin resistance. In addition, these patients showed increase of lipoprotein and general glutathione concentration in serum. The authors made a conclusion that prescription of vitamin D together with calcium during 12 weeks has positive effect on glycemic profile, concentration of cholesterine, and prevents development of gestation diabetes [33].

The meta-analysis of randomized controlled studies conducted in 2017 allowed determining the interrelation between the low level of maternal 25[OH]D and preterm birth development. The effectiveness of 25[OH]D taking to decrease the preterm birth is shown [34].

Other researchers have also obtained favorable results on vitamin D deficiency correction for women with a history of miscarriage. The results of the prospective cohort study of 1683 pregnant women showed the interrelation between 25[OH]D concentration in maternal serum and a risk of follow-up miscarriage. Under vitamin D deficiency there were 58 spontaneous miscarriages during the first trimester of pregnancy. However, there were no miscarriages under vitamin D high concentration (more than 20 ng/ml). These data confirm the reasonability of vitamin D intake during the preconception period to prevent spontaneous miscarriages [22].

The research results show the effectiveness of vitamin D prescription in preventing the symptoms of bacterial vaginosis [22].

If during the first trimester of pregnancy the patients have vitamin D deficiency, the risk that a newborn will have the growth and body mass deficiency increases twice. Baker A.M. et al. [35] have examined 2146 women for the vitamin D level during the first or second trimester of gestation period, state of newborns after birth, and the weight of placenta. The research results showed that vitamin D deficiency causes the decrease of D-receptors level in the placenta that in turn leads to preterm uncontrolled apoptosis of placenta cells, development of placental insufficiency, retarded intrauterine growth, and low Apgar score for newborns. Close interrelation between a mother and her fetus leads to the fact that insufficiency of vitamin D during pregnancy causes its deficiency in a child's body starting from his fetal life. But even those newborns whose mothers had sufficient vitamin D concentration, in eight weeks after the birth start to experience its deficiency if the nutrition is not supplemented with this vitamin [36-38].

Hossain N. et al. have studied the effect of vitamin D on birth outcomes for newborns and found that Apgar score at 1-st and 5-th minute after birth is higher for those born by mothers who took vitamin D in comparison to babies whose mothers did not take it ($p = 0.03$ and $p = 0.05$, respectively) [39].

The contemporary scientific literature presents various information regarding optimal level of vitamin D for pregnant women, its deficiency and insufficiency.

Clinical significance of serum 25[OH]D increased concentration is not clear yet. The conducted researches do not have any information on unfavorable consequences of serum 25[OH]D high concentration. Therefore, the question on necessity to give vitamin D as a part of preconception preparation and during pregnancy to all women to improve maternal and perinatal outcomes remains open and requires further investigation [31, 40].

In this regard, it is scientifically and practically necessary to continue studies on vitamin D significance during the gestation period.

Thus, vitamin D has very large perspectives in optimizing the health state of pregnant women in a risk group, and children. Preventive measures regarding vitamin D during pregnancy and achievement of optimal level of calcium from the childhood allows not only to prevent rickets, but also decrease a risk of osteoporosis and other long lasting latent disease processes caused by vitamin D deficiency during pregnancy. This measure is one of the most important preventive programs of the healthcare system. It is necessary to conduct further researches to precise adequate level of vitamin D concentration, its effect during pregnancy and birth, and determine vitamin D dose that will be enough to improve maternal and perinatal health.

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