The Prevalence of Vitamin D Defficiency and its Obstetrical Effects

A prospective study on Romanian patients

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The birth, growth, development, reproduction and senescence under physiological conditions can be achieved without diminishing the role of other important aspects that influence them, only with the support of an optimal diet that is a fundamental requirement nowadays, considering that the health and the nutritional status are in a permanent interdependence. The effects of inadequate nutrition reflect on the expression of genes, influencing the development of certain diseases in childhood and adulthood. Knowing the phases of the gestation period in which the need of certain nutrients is increased, and their absence has the most serious impact on fetal growth and development, allows for the adoption in due time of concrete preventive rules. Disorders associated with lipid malabsorption, such as celiac disease, Crohn's disease, pancreatic insufficiency, cystic fibrosis and cholestatic disease, are associated with low serum levels of 5-hydroxyvitamin D. Vitamin D deficiency in the newborn can express as deficient skeletal homeostasis, congenital rickets and fractures in the early days of life. A low level of vitamin D during pregnancy seems to increase the risk of preeclampsia, intrauterine growth restriction and gestational diabetes, and in the longer term it seems to affect the bone, immune system and general status. The prevalence of hypovitaminosis D is increasing globally, and the effects on pregnancy and neonatal outcome of the vitamin D deficiency and supplementation are a topical issue, which is currently under investigation.

Keywords: vitamin D, pregnancy, deficiency.

Pregnancy is a particular physiological situation through the impact on the individual, the family, but also on society. The current concepts and orientations referring both to the pre-conceptional nutrition of the woman in the fertile period and to the nutritional intake during pregnancy target its effects on the conception product. The gestational state is a period of intense fetal growth and development and major adaptive changes in the maternal body. Malnutrition, both in the sense of deficit and excess, is associated with unfavorable results of pregnancy evolution, which is why it is of particular importance to evaluate, monitor and permanently improve the nutritional status of women [1], both during pre-conceptional period and during pregnancy and lactation.

The objectives of our study were to establish the incidence of vitamin D deficiency in a sample of Romanian pregnant women in the first trimester of pregnancy and in women with infertility and to compare the incidence of obstetrical and neonatal outcomes in women with and without vitamin D (cholecalciferol) supplementation with doses of 400 UI and 1400 UI.

Biochemical mechanisms

The effects of inadequate nutrition reflect on the expression of genes, influencing the development of certain diseases in childhood and adulthood [2,3].

Vitamin D or Calciferol is a generic term comprising a group of liposoluble compounds having a skeleton composed of four cholesterol molecules. The 25-hydroxyvitamin D is the major circulating form of vitamin D. The half-life is 2-3 weeks compared to the 24 h of the inactive vitamin D form. The 25 (OH) D activates in the bone and intestine but represents below 1% of the potency of 1,25 dihydroxy vitamin D, representing the highest activity form of this vitamin, whose half-life is 4-6 h. The 1,25-dihydroxyvitamin D binds to intracellular receptors present in target tissues and regulates gene transcription, a mechanism that is realized with a single receptor (VDR), universally expressed in nucleated cells.

Vitamin D is obtained from dairy products, vegetables, fish oil and dietary supplements. The endogen vitamin D is produced by direct exposure to the sun [4].

Previtamin D is synthesized non-enzymatically in skin from 7-dehydrocholesterol during exposure to ultraviolet light in sunlight. Previtamin D is subsequently subjected to temperature-dependent conformational rearrangement, forming vitamin D3 (cholecalciferol). This system is excessively effective, with the estimated occasional exposure of just arms and face to the sun being equivalent to the ingestion of 200 international units (IU) per day. However, it is difficult to assess the duration of daily exposure required to obtain the equivalent of oral vitamin D supplementation, as there are many variables represented by skin type, latitude, season and time of the day. Prolonged exposure of the skin to sunlight cannot produce toxic amounts of vitamin D3 due to the photo

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conversion of pre-vitamin D3 and vitamin D3 in inactive metabolites (lumisterol, tahisterol, 5,6-transvitamin D and suprasterol 1 and 2). In addition, sunlight induces melanin production that reduces vitamin D 3 production in the skin [5,6].

Children, people with disabilities and the elderly may experience inadequate sun exposure and the dermis of people over the age of 70 is no longer able to efficiently convert vitamin D. Vitamin D present in the diet is incorporated into the mycelium, absorbed by enterocytes and then stored in chylomicrons. Disorders associated with lipid malabsorption, such as celiac disease, Crohn's disease, pancreatic insufficiency, cystic fibrosis and cholestatic disease, are associated with low serum levels of 5-hydroxyvitamin D [7].

Vitamin D from diet or dermal synthesis is biologically inactive and requires enzyme, liver and kidney conversion to generate active metabolites (fig. 1).

Dietary vitamin D is directed to the liver linked to the vitamin D binding protein associated permanently with chylomicrons and lipoproteins. Along with endogenously synthesized vitamin D3, exogenous vitamin D is metabolized into the liver, where the hepatic 25-hydroxylase enzyme places a hydroxy group at the 25-position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D (25 [OH] D, calcidiol); 25-hydroxyvitamin D2 has a lower affinity compared to 25-hydroxyvitamin D3 for the vitamin D binding protein. Therefore, 25-hydroxyvitamin D2 has a half-life shorter than 25-hydroxyvitamin D3. In this context, vitamin D2 treatment is not able to grow total serum level of 25 [OH] D as effective as vitamin D3 [8]. An adequate vitamin D level during pregnancy ensures an optimum vitamin D level to the fetus, resulting in a normal bone development due to the fact that vitamin D crosses the placenta and creates deposits especially during the 3rd trimester. A vitamin D deficit in women during pregnancy is most prevalent in high risk populations [9]. Low levels of vitamin D in pregnancy seems to be associated with an increased risk for gestational diabetes mellitus, preeclampsia and fetal growth restriction and in the long term, for deficient skeletal homeostasis, congenital rickets, early bone fractures and immune deficiencies [10-12].

The American College of Obstetricians and Gynecologists considers vitamin D deficit a circulant 25(OH) vitamin D level below 32ng/mL (80mmol/L). Normal serum vitamin D level in pregnancy is considered to be around 30 ng/ml, with a minimum accepted level of 20ng/ml. Generally, medical laboratories measure the total concentration of 25(OH) vitamin D. Since 2010, there is an international program of standard 25(OH)D measurement, which aims to obtain a gold standard measurement method applying evaluation procedures developed by the National Institute for Standards and Technology, Ghent University and Centre for Diseases Control and Prevention (CDC) [13]. The Institute of Medicine (IOM) recommended in 2010 a supplementation with 600 UI/day of vitamin D in all women of reproductive age, including pregnant and lactating women [14]. In 2011 and in 2017 the ACOG recommends vitamin D supplementation with only the usual dose contained by prenatal vitamin supplements with no further increase of dosage unless serum decreased levels occur. A daily intake up to 2000 UI of Vitamin D during pregnancy seems safe if levels above 30 ng/ml are targeted. In fact, the intake of a sufficiently higher dose in pregnancy was never studied, being only speculated that a 600-800 UI/daily should be safe and adequate [13].

Among studies on efficiency and safety of vitamin D supplementation in pregnancy, Yu CK et al. investigated vitamin D supplementation with single daily oral dose of 200.000 UI or 800 UI in pregnant women with gestational age above 27 weeks and vitamin D deficiency. Both dosage alternatives resulted in an improvement of vitamin D levels, but in an insufficient population, leading to the necessity of further studies on optimal dosage and moment of administration [14-16]. Dawodu et al studied vitamin D supplementation in pregnancy in a population with endemic deficiency using daily prenatal supplements with 2000 UI and 4000 UI compared to 400 UI/ day. Administration was randomly started at 12-16 weeks and continued up to delivery. Most efficient and safest dose was found to the of 4000 UI [17]. Most meta-analysis studies conclude that the studies are insufficient and of low data quality. Therefore, a final conclusion on the appropriate dosage and moment of administration of vitamin D supplements in pregnancy for the prevention of vitamin D deficiency could not be drawn. Initiation of vitamin D supplementation prior to pregnancy was not studied.

Recommended Dietary Allowance (RDA) for vitamin D in pregnancy and lactation is 600 UI (15 mcg/day). The majority of prenatal supplements contain 400 UI of vitamin D, but this dose is considered insufficient for those women who have low vitamin D levels at the beginning of pregnancy. On the other hand, the toxic level of vitamin D has not been yet established. IOM defines a vitamin D tolerable upper intake level at 4000 UI (100 mcg) daily for healthy adults, children between 9-18 years old and pregnant and lactating women. In patients with a normal

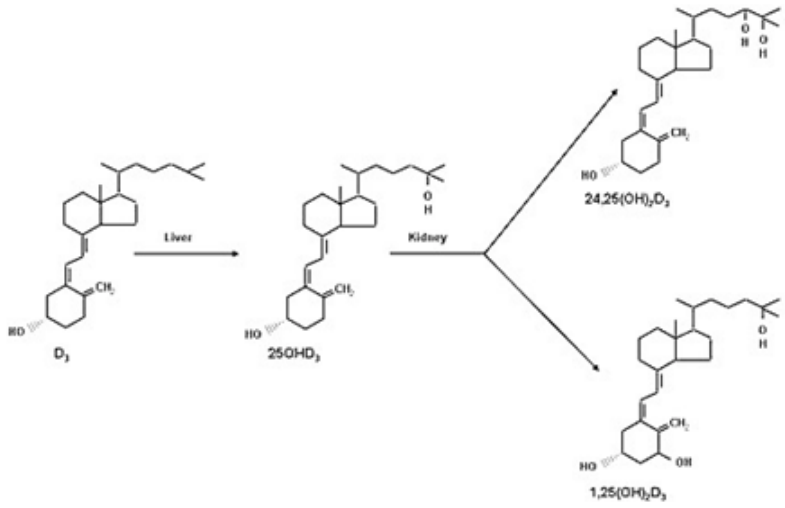

Fig. 1. Chemical structure of vitamin D metabolites.

absorption capacity, the serum 25(OH)D level increases with 0.7-1 ng/ml for every 100 UI intake. Patients with lower base levels have a higher increase. Patients with malabsorption require individual supplementation dosage, some of them up to 50.000 UI and monitoring for vitamin D toxicity. Vitamin D intoxication was documented in adults with an intake above 60.000 UI/day. A meta-analysis of seven clinical trials concluded that cholecalciferol is superior to ergocalciferol for increasing serum 25(OH)D levels [18].

Experimental part

Materials and Method

The sample included pregnant patients, non-pregnant patients who were admitted for infertility, non-pregnant patients without fertility issues who were admitted for a yearly routine check-up. Age ranges: 16-80 years old. Timeframe: January 2015 to December 2017.

Pregnant patients were categorized into two groups: patients who did not receive vitamin D supplements and patients who received vitamin D supplements. Part of those who received vitamin D, received 400UI/day in the second trimester and those who were found to have a vitamin D deficit < 30ng/ml received 400UI+1000UI daily. Non-pregnant patients and patients who dealt with infertility received 1000UI vitamin D only if low concentrations were found.

Inclusion criteria

-Non-pregnant women who comply to treatment and follow-up visits for 1 year.

-Pregnant women with gestational age < 13 weeks, who comply to treatment and follow-up visits for 1 year.

Exclusion criteria

-Women who already received vitamin D supplements

-Women with certified vitamin D malabsorption syndromes

-Women with current missed abortion or non-viable pregnancy

-Women with adnexal tumors or renal lithiasis

-Women with heart disease

-Pregnant women with hypertension and diabetes

-Pregnant women with a history of preterm birth

Patient evaluation

1.First visit: evaluation for patient eligibility

2.Evaluation visit: evaluation of blood tests samples and initiation of vitamin D supplementation. Pregnancy status evaluation. Schedule of next appointment for vitamin D levels assessment after 3 months supplementation. Evaluation of vitamin D levels for 20 weeks pregnancies.

3.Final visit: 37 weeks pregnancies. Ultrasound examination for pregnancy evaluation.

4.Birth registration and newborn follow-up: gestational age, delivery mode, pregnancy outcomes, fetal weight and length, Apgar score, fetal outcomes. Mothers were asked about newborn signs of rickets at 6 months.

Vitamin D levels were assessed at Medlife Laboratories for all patients. Database was accessed after obtaining the Ethical Committee agreement.

Results were categorized as follows:

-Severe hypovitaminosis < 9.99 ng/mL.

-Moderate hypovitaminosis: 10-19.99 ng/mL.

-Light hypovitaminosis: 20-29.99 ng/mL.

-Normal vitamin D level >30 ng/mL.

Results and discussions

A total of 77 patients were included in our study: 40 pregnant women and 37 non-pregnant women.

Among patients with vitamin D deficiency, only 12 came back for a second evaluation after treatment. Lack of compliance due to high treatment costs was the main reason for the patients did not continue follow-up visits.

Analyzing the entire patient sample, we noted 84.4% had vitamin D deficiency. The medium vitamin D level was 20.89 ng/mL, minimum level was 6.3 ng/mL and the maximum level was 56.5 ng/mL (fig 2).

According to literature studies, vitamin D hypovitaminosis among adult women is 41-42%, but in Romania this is double. Moreover, a smaller percentage of pregnant women have normal vitamin D levels (12.5%) as compared to non-pregnant women (18.9%). Therefore, vitamin D supplementation in pregnancy is justified. Vitamin supplements are only optional, the only national program available is iron supplementation for anemia prophylaxis in pregnant women.

Initial vitamin D levels did not statistically correlate with season, age, marital status or gestational age, although the autumn samples had slightly lower vitamin D levels as compared to samples taken during summer.

In the pregnancy group, we investigated the correlation between vitamin D level and pregnancy outcomes (gestational, hypertension, preeclampsia, gestational diabetes, preterm birth) (fig. 3,4,5). The only statistically significant negative correlation found was between supplementation with higher vitamin D dosage (1400UI/

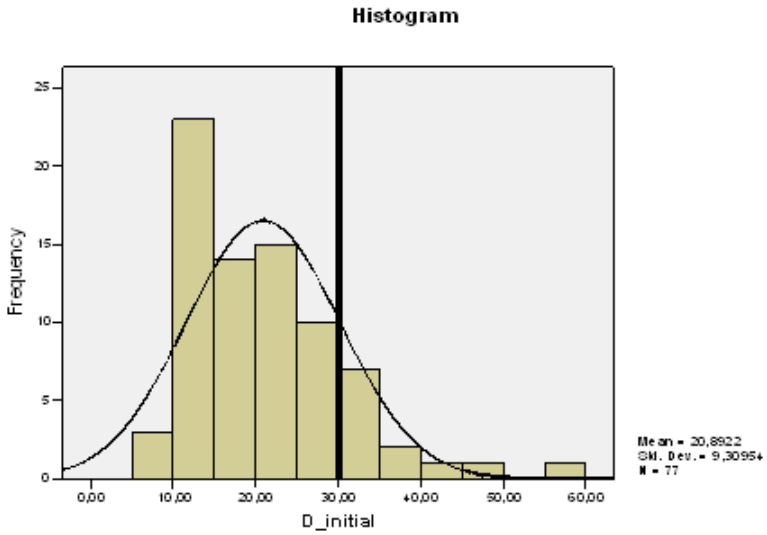

Fig 2. Distribution of vitamin D levels at first measurement.

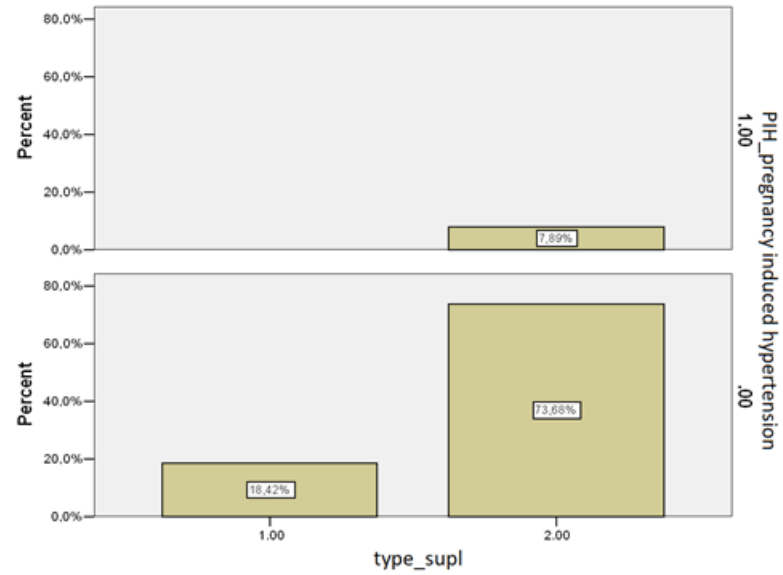

Fig. 3. Correlation between vitamin D supplementation and pregnancy-induced hypertension.

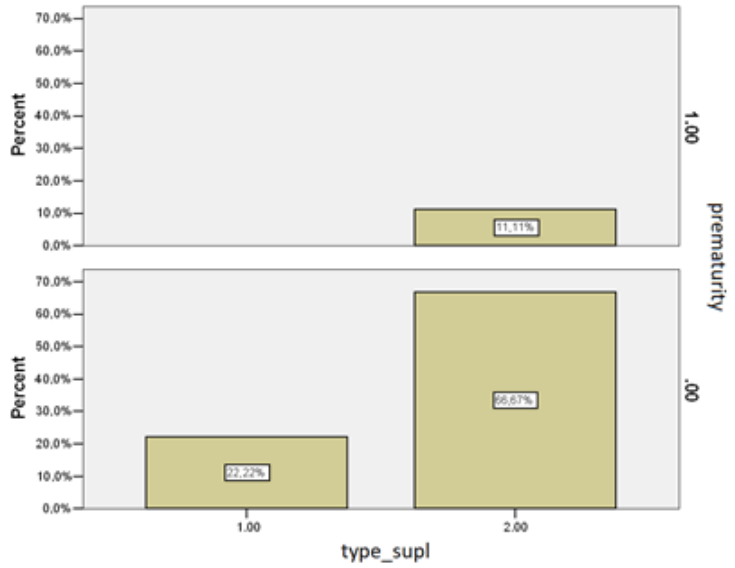

Fig. 4. Correlation between vitamin D supplementation and preterm birth

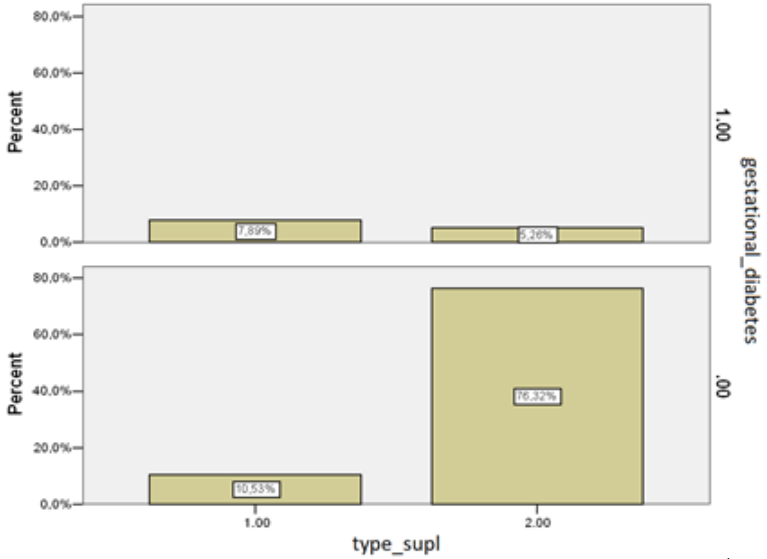

Fig. 5. Correlation between vitamin D supplementation and gestational diabetes mellitus

day) and the reduction of gestational diabetes risk (R=-.417, p=.009). A positive correlation was found between the rate of spontaneous abortion and fetal birthweight.

We noted that among pregnant women with no vitamin D supplementation in first trimester, only 15.58% had normal vitamin D levels; the majority had moderate vitamin D deficiency (vitamin D levels 10-19.9 ng/mL). This sample can be extrapolated to the Romanian non-pregnant female population. Severe hypovitaminosis was found in 4% of patients (fig. 6). Patients with mild to moderate Vitamin D deficiency reached normal levels after 2 months of therapy.

In the infertility group we compared median vitamin D levels to those in the fertile group (fig. 7).

The optimum serum level of 25(OH)D in pregnancy is unknown. American medical societies recommend routine measurement of vitamin D levels for obese pregnant women who wear sun-protective clothing, who have a history of vitamin D malabsorption or other risk factors for vitamin D deficiency. ACOG and Endocrine Society

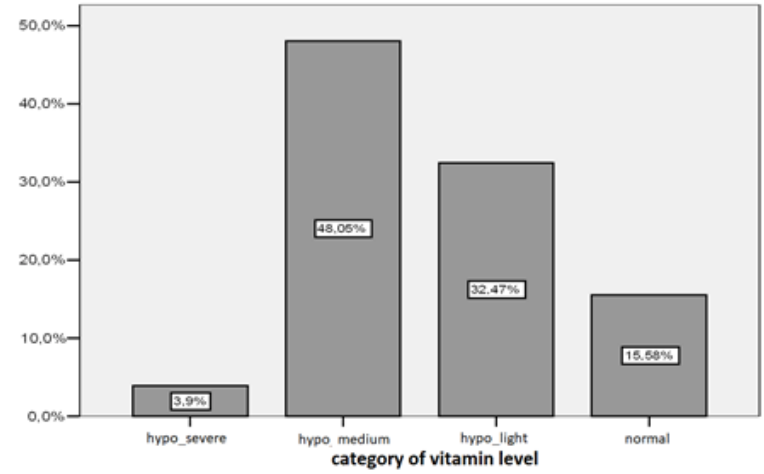

Fig. 6. Distribution of vitamin D hypovitaminosis degrees in patient sample

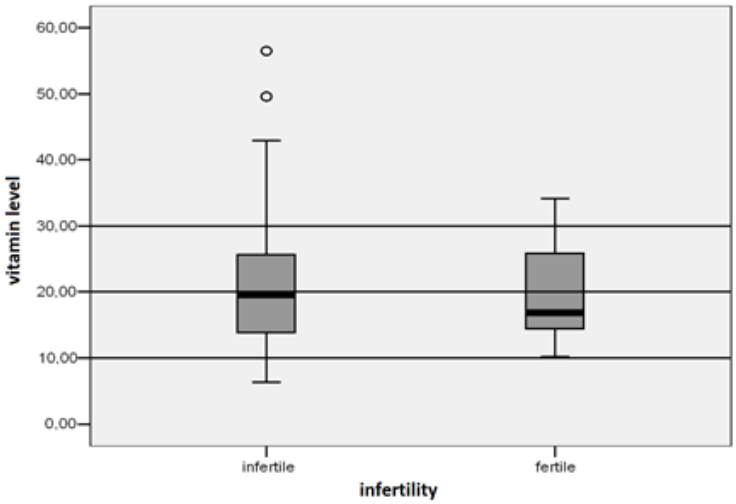

Fig. 7 Median levels of vitamin D in fertile patients compared to infertile patients.

demonstrated that vitamin D deficiency in pregnancy can be safely treated with 1000-2000 UI/day. This is the reason we decided vitamin D supplementation with 1000 UI/day in our study.

Observational studies suggest an association between vitamin D deficiency and pregnancy complications [19-22]. A metanalysis of 31 studies, by Aghajafari et al concluded there is an increased risk for gestational diabetes, preeclampsia and intrauterine growth restriction in vitamin D deficient women [23]. The studies do not mention a clear relation between dosage and treatment response. A prospective study on 3960 mother and child pairs of European patients correlated 25(OH)D levels in the mothers to bone densitometry of their 9-10 years old children. No significant correlations were found in this study, but smaller studies found correlations in the descendants at the age of 20. In our study, we did not find any rickets case in the first 6 months. A metanalysis of 13 trials published in 2015 (Avon Longitudinal Study of Women and Children) found no associations between vitamin D supplementation, time of treatment initiation and the risk for gestational diabetes, preeclampsia, low birthweight and preterm birth [24-26].

In 2016 De-Regil et al published in the Cochrane Database a review on vitamin D supplementation for women during pregnancy. The 15 trials included 2833 women with multiple confounding factors. The study found that a normalization of vitamin D levels with daily continuous supplementation lowers the risk for preeclampsia, but the final recommendation was that more rigorous studies were required [27]. In our study, we found correlations only with gestational diabetes. Data from other trials suggest a similar risk for gestational diabetes in pregnant patients with or without vitamin D supplementation.

According to other studies, vitamin D supplementation during pregnancy reduces the risk for preterm birth and it also lowers the incidence of low birth weight newborns [28,29]. Concomitant vitamin D and calcium supplementation seems to significantly reduce the risk for preeclampsia, but it increases the risk for preterm birth [30,31]. There is no clear data regarding time of supplementation in any study [32,33].

Conclusions

Vitamin D deficiency is significantly present during pregnancy and in infertile patients. In Romania, the prevalence of such deficiency is twice higher than in the US. The supplementation with 400 UI/day is not sufficient to maintain normal vitamin D levels. Vitamin D deficiency was significantly statistically correlated with gestational diabetes only. More studies are required on the optimal dose for infertile women and also for pregnant women. Moreover, more trials are required to see if vitamin D supplementation in early pregnancy influences maternal and fetal outcomes. More data is needed to confirm safety and efficacy for higher vitamin D doses in pregnant women with high vitamin D deficiency.

Until new clinical results are available, we propose vitamin D level measurement in all pregnant women and also in infertile women and if deficiency is found, we recommend supplementation with a minimum dose of 1000 UI daily.

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