

ROLE OF THE HORMONAL SYSTEM “VITAMIN D/VITAMIN D RECEPTORS” IN THE FORMATION OF SOME PREGNANCY COMPLICATIONS

INTRODUCTION

The latest findings demonstrate that biological role of hormonal system “vitamin D/vitamin D receptor” (VD/VDR system) is not limited to its classical effect on bone-mineral metabolism. It was ascertained that calcitriol as a classical steroid hormone involved in the regulation of a number of physiological processes by auto-, para- and endocrine pathways, and discovery of more than 2200 genes encoding its receptors in many organs and tissues and controlling more than 3% of human’s genome allowed us to state that VD lack or deficiency is associated with a number of diseases that are not associated with its participation in calcium homeostasis regulation [1, 8, 12]. The most investigated non-classical effect of calcitriol is its ability to modulate immune, endothelium-dependent, antiproliferative and other reactions associated with diseases of cardiovascular system (arterial hypertension), diabetes mellitus, skin diseases, bronchial asthma, oncological diseases [19, 22].

Literature data indicates not only the widespread prevalence of VD deficiency in the world, but also the possibility of influencing the development of calcitriol-associated diseases through its supplements [3, 4, 23].

VD receptors are widely presented immediately in the ovaries, uterus, trophoblast, placenta and in other organs of the reproductive system. Taking into account epidemiological aspects of VD lack and deficiency, their effect on the functional state of the reproductive system seems logical. Studies of VD role in the pathomechanisms of the formation and development of the reproductive system organs various diseases, as well as pregnancy complications, are one of the important directions of modern reproductive, obstetrics and prenatalology [2, 9, 20].

Purpose of the study: to determine VD status and its effect on the course of gestational process in the women dwelling in the southern region of Ukraine.

MATERIALS AND METHODS

459 women were examined. Examinations were made at the base of the public utilities “Maternity Hospital No. 1” and “Maternity Hospital No. 5” (Odesa, Ukraine) from 2016 till 2019. All the persons under examination gave informed consent.

Exclusion criteria were the presence of severe extragenital pathology (diabetes mellitus, chronic kidney and liver diseases with insufficiency), impaired fat metabolism, skin diseases, autoimmune diseases, thyroid and parathyroid glands diseases, which can have a significant effect on the metabolism and level of VD in blood serum.

It should be noted that all patients took one or another complex of multivitamin - mineral complexes containing VD (in general, none of the received complexes contained more than 500 IU VD).

General clinical examination of pregnant women, clinical and laboratory tests to assess the fetus’s condition and uteroplacental-fetal circulation (ultrasound, Doppler, hormonal, and other methods) were carried out in accordance with the requirements of regulatory documents in the prescribed period of pregnancy and/or according to indications.

The studies were carried out in the gestational age of 28–34 weeks, in spring to exclude the influence of the seasonal factor to the level of solar insolation and the presence of equal conditions for dermal VD synthesis.

VD status was determined by enzyme-linked immunosorbent assay (ELISA) based on the principle of competitive binding (at level 25(OH)D in blood serum) on a COBAS Integra 400 Plus analyzer (Roche Diagnostics, Switzerland). 25(OH)D is the main circulating metabolite of both forms of VD and its level can be quantified.

When determining the status of VD we were guided by the “Guidelines for Preventing Deficiency Vitamin D in the Population of Central Europe” [24]. According to this Guidelines VD deficiency is defined as 25(OH)D <20 ng/ml (50 nmol/L), VD deficiency (suboptimal status) – if 25 (OH)D are 21–30 ng/ml (50–75 nmol/L), optimal or adequate level of VD – 30–50 ng/ml (75–125 nmol/L), high level of VD is considered when its values in blood serum are higher than 50 ng/m (125 nmol/L).

All statistical analyzes were performed using Biostat, Statistica 6.0 software from Install Shield Software Corporation (USA).

RESULTS

Take account of the seasonal fluctuations in VD level associated with the level of solar insolation it should be noted that the Odesa region, Kherson and Nikolaev regions of Ukraine are charac-

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terized by the highest average annual level of solar insolation ($3.55 \text{ kW}\times\text{h}/\text{m}^2 \times \text{day}$) compared with the regions where the corresponding indicator is the lowest among the regions of Ukraine: Lviv region – $2.92 \text{ kW}\times\text{h}/\text{m}^2 \times \text{day}$, Chernivtsi region – $2.98 \text{ kW}\times\text{h}/\text{m}^2 \times \text{day}$. All pregnant women were residents of Odesa that allows us to conditionally assume optimal states for the synthesis of VD active metabolite.

The average age of the patients was 30.35 ± 3.12 years; they all were normotrophs with an average body mass index $22.8 \pm 1.93 \text{ kg}/\text{m}^2$.

VD status determined. It was found that only a third of pregnant women (141 or 30.7% of 459 women) who made up the control group had an optimal serum VD level ($43.38 \pm 9.67 \text{ ng}/\text{ml}$) or adequate to ensure its biological effects.

The main group consisted of 318 (69.3% out of 459) pregnant women with a VD level corresponding to deficiency status ($25.45 \pm 4.63 \text{ ng}/\text{ml}$ on average in 229 women out of 459 – 49.9%) and deficient status ($15.28 \pm 4.78 \text{ ng}/\text{ml}$ in 89 or 19.4% out of 459) (Fig. 1).

Women with a serum level of 25 (OH) D above $50 \text{ ng}/\text{ml}$ ($125 \text{ nmol}/\text{L}$) were not found among the persons under examination.

Groups were homogeneous according to the intergenetic interval and the parity of labor. 70.7% were primiparous in the main group (225 out of 318 women), 66.7% in the control group (94 out of 141 women); ($F = 0.65, p \geq 0.05$), multiparous (2nd and 3rd births) accounted for 29.3% and 33.3% respectively in the main and control groups ($F = 0.65, p \geq 0.05$). The average interval between births in multiparous patients was 3.7 ± 2.5 years.

Obstetric and gynecological history in the main group was characterized by a significantly higher frequency of gynecological diseases.

3.5% of women (11 people out of 318) in the main group has scleropolycystic ovary syndrome, pregravid hypoplasia of the uterus, Asherman's syndrome, there were no such patients in the control group ($p < 0.001$). Inflammatory diseases of the uterine appendages were observed in 10.06% (32 of 318) and 2.8% (4 women) in the main and control groups ($F = 0.082, p \geq 0.05$).

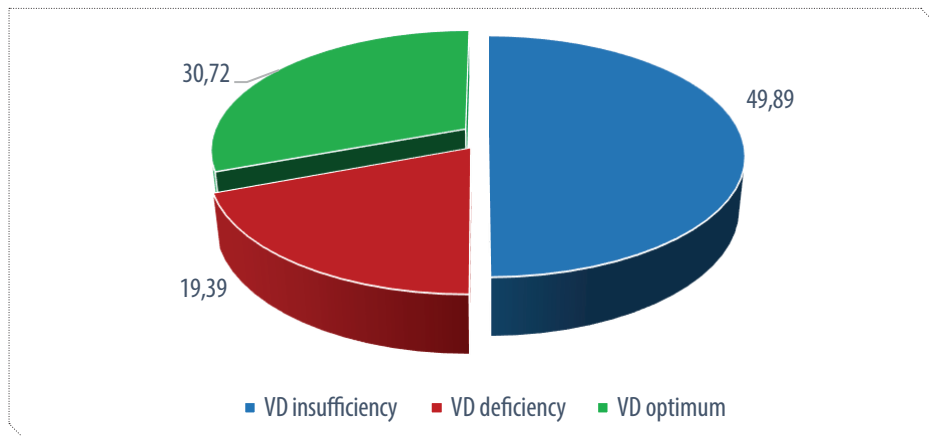


Figure 1. VD status of pregnant women, %

Background diseases of the cervix were diagnosed in 26.7% (85 of 318 women) and 5.7% (8 of 141) women respectively ($F = 0.0001; p < 0.01$). 9.74% (31 of 318) patients of the main group had uterine fibroids, in the control group there were no such patients ($F = 0.0015; p < 0.05$).

Miscarriage was indicated by more than a quarter of women in the main group (26.7% or 85 out of 318); in the group with optimal VD status such patients were significantly less (3.5% or 5 out of 141) ($F = 0.00001; p < 0.01$).

The course of pregnancy was characterized by a significantly higher frequency of various complications in the group of pregnant women with insufficient and VD deficient status (Fig. 2).

With regard to the threat of pregnancy termination and premature delivery 45.6% of patients in the main group were treated, and only 9.9% of women in the control group ($F = 0.00001; p < 0.01$). Gestational data were observed in 10.06% and in 4.3% ($F = 0.164; p \geq 0.05$) pregnant women in the main and control groups, pregnancy was complicated by preeclampsia in 13.5% of patients with suboptimal and deficient VD status, and in 2.8% with its optimal status ($F = 0.0093; p < 0.05$). Grade 1–2 anemia was 2.5 times more often diagnosed in the main group (43.7% and 20.6%) ($F = 0.0008; p < 0.01$). Incidence of acute respiratory viral infections in the main group was quite high

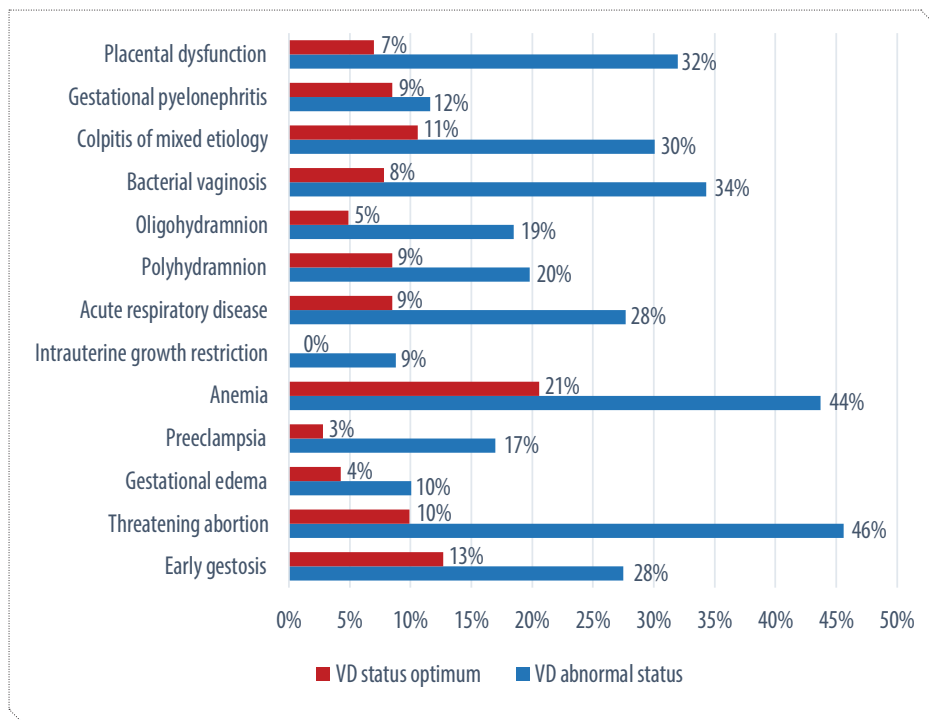


Figure 2. Frequency of pregnancy complications in pregnant women with normal VD levels in the blood and in pregnant women with VD insufficient and deficient levels

compared with the comparison group (27.7% and 8.5% respectively) ($F = 0.0009$; $p < 0.01$).

Placental dysfunction developed in 4.5 times more often with insufficient VD in the blood (32% and 7% respectively in groups) with 9% realization in the intrauterine growth retardation syndrome (28 of 318 women; $F = 0.00001$; $p < 0.01$). Fetus's retardation was not diagnosed in the comparison group.

A high incidence of inflammatory diseases and an imbalance of vaginal biocenosis were detected in pregnant women with suboptimal and deficient VD status: 64.4% versus 18.4% ($F = 0.00001$; $p < 0.01$). Urogenital tract biocenosis was characterized by a significantly lower frequency and insignificant degree of colonization by infectious agents in patients with an optimal VD level and a physiological course of pregnancy (maximum 10^3 CFU/ml).

The presence of polyhydramnios (19.8% and 8.5%; $F = 0.015$; $p < 0.05$) or low water (18.5% and 4.9%; $F = 0.0039$) also points to inflammatory changes in extraembryonic formations ($p < 0.01$).

Polyhydramnios was observed 2.8 times more often and oligohydramnion almost 8 times more often in patients with placenta dysfunction.

DISCUSSION OF THE RESULTS

The data of a high incidence of VD deficiency/shortage in pregnant women dwelling in a region with high levels of solar insolation are probably a reflection of general population-based behavioral characteristics, in particular a commitment to the widespread use of sunscreens, on the one hand, and a limited time spent in the sun, on the other hand, which leads to a decrease of cholecalciferol synthesis in the skin [13, 16].

The presence of VDR directly on the body's immunocompetent cells (monocytes, macrophages, dendritic cells and lymphocytes) indicates the participation of VD in the reactions of innate and acquired immunity [6].

Under the conditions of VD-deficiency a violation of the immunological balance is observed, in particular, the production of antimicrobial peptides (defensin and cathelicidin) directly in the placenta is inhibited, that may cause activation of chronic inflammatory diseases or the formation of primary foci of infection; in particular a correlation between the frequency of bacterial vaginosis and low VD in the blood of pregnant women was revealed [11, 21]. According to our data, a violation of the vaginal biocenosis under the conditions of insufficient VD level was observed 3.5 times more often.

VD's immunomodulatory properties also explain its role in the pathogenesis of immature pregnancy by regulating the expression of VDR in activated T-cells, in the production of T-regulatory cells (T-suppressors) and T-helpers (Th17) which are necessary to ensure immunological tolerance during normal pregnancy. At VD's deficiency, under the conditions of T-suppressors decrease, number of pro-inflammatory Th17 increases – the balance between pro- and anti-inflammatory cytokines is violated, followed by activation of nonspecific inflammatory processes which is realized in immature pregnancy [7, 14]. Almost half of the pregnant women with a suboptimal level of VD had clinical signs of pregnancy interruption, while in women with optimal VD status; only every 10th patient was treated in connection with this diagnosis.

Calcitriol has a dose-dependent ability to suppress the inflammatory process in the trophoblast activated by pro-inflammatory cytokines: in this case, the auto- and paracrine pathways modulate the immune relations between the mother's and embryo's bodies [17].

A reliably high frequency of amniotic membrane dysfunction with a change in the amount of amniotic fluid in the group of insufficient VD pregnant women indicates a high risk of intrauterine infection in these patients.

According to our data, a significantly higher frequency of preeclampsia and placental dysfunction in women with violated VD status indicates pathological angiogenesis and abnormalities in the pace and structural changes of the spiral arteries.

It is known that calcitriol has a dose-dependent effect on trophoblast invasion: decrease in the rate of gestational transformations in the vessels even at the stage of decidual changes and signs of insufficiency of vascular invasion of syncytiotrophoblast, insufficient morphological transformations of the spiral vessels of the uterus lead to a decrease in the total area of the intervillous space, formation and development of placental pathological hypoxic-ischemic changes [5]. This may explain preeclampsia's high frequency.

In addition, VD/VDR system can lead to impaired endometrial receptivity and formation of primary chorion and placenta dysfunction with pathological implantation and impaired perfusion of the placenta. In their turn, these changes are also the initial stage in the formation of placenta dysfunction [18]. Later on placental ischemia and systemic endothelial dysfunction lead to multisystem disorders with the development of a complex of multi-organ changes specifically attributed to preeclampsia. Risk of severe preeclampsia increases by 4–5 times if there are VD deficiency (≤ 20 ng/ml). 25(OH)D concentration in blood serum in patients with preeclampsia is by 23% lower than in women with physiological pregnancy [10, 15].

CONCLUSIONS

Information on the multifunctionality of the VD/VDR hormonal system, its participation in the regulation of angiogenesis, cellular apoptosis, immunological reactions and other physiological and pathological processes in a human body allow us to talk about VD role in the pathogenetic mechanisms of the formation and development of various complications of the gestational process.

For the first time in the Odesa region VD status in pregnant women an epidemiological study was conducted and it was established, that 70% of them under living conditions with the highest average annual level of solar insolation compared with other regions of Ukraine, have insufficiency or VD deficiency.

Pregnancy at the background of suboptimal or VD deficiency status is characterized by a significantly higher frequency of preeclampsia (4.8 times more often, $F = 0.0093$; $p < 0.05$), placental dysfunction (4.5 times), risk of premature labor (4.6 times more often, $F = 0.00001$; $p < 0.01$), intrauterine infection clinic (2.8 times more often, $F = 0.0039$; $p < 0.01$), gestational anemia (2.5 times more often, $F = 0.0008$; $p < 0.01$).

Further studies on the possibility of preventing complications of the gestational process by correcting of VD status are advanced research directions.

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Introduction. The hormonal system "vitamin D/vitamin D receptors" (VD/VDR) is involved in the regulation of numerous physiological processes. VD lack or deficiency is associated with a number of different diseases, including pregnancy complications.

Purpose of the study: to determine VD status and its effect on the course of the gestational process in women from the southern region of Ukraine.

Materials and methods. 459 women were examined, 318 (69.3%) of them were the main group and 141 (30.7%) were the comparison group.

In addition to standard general clinical examinations, ELISA on a COBAS Integra 400 Plus analyzer (Roche Diagnostics, Switzerland) the VD level was determined in the blood.

Results and discussion. 49.9% of the pregnant women in the main group had insufficient VD level (25.45 \pm 4.63 ng/ml), in 19.4% it corresponded to a deficit (15.28 \pm 4.78 ng/ml). VD concentration in the comparison group was 43.38 \pm 9.67 ng/ml ($p < 0.01$). Significantly more frequent pregnancy complications in the main group were threatening abortion (45.6% VS 9.9%; $F = 0.00001$; $p < 0.01$), preeclampsia (13.5% VS 2.8%; $F = 0.0093$; $p < 0.05$), placental dysfunction (32% VS 7%; $F = 0.00001$; $p < 0.01$), vaginal dysbiosis (64.4% VS 18.4%; $F = 0.00001$; $p < 0.01$), pregnant anemia (43.7% VS 20.6%; $F = 0.0008$; $p < 0.01$) and signs of inflammation of the amniotic membranes (38.3% VS 13.4%). Syndrome of intrauterine growth retardation diagnosed in 9% women in the main group; in the comparison group none case was noted.

Conclusion. 70% of pregnant women in Odessa region have a lack or deficiency of VD. Pregnancy course is characterized by a significantly greater frequency of preeclampsia (4.8 times more often), placental dysfunction (4.5 times), threat of miscarriage (4.6 times more often), intrauterine infection (2.8 times more often), gestational anemia (2.5 times more). It seems promising to conduct further research on the possibility of preventing complications of the gestational process by correcting VD status.

Keywords: vitamin D hormone, vitamin D receptors, pregnancy complications, preeclampsia, placental dysfunction.

РОЛЬ ГОРМОНАЛЬНОЙ СИСТЕМЫ «ВИТАМИН D/РЕЦЕПТОРЫ ВИТАМИНА D» В ФОРМИРОВАНИИ НЕКОТОРЫХ ОСЛОЖНЕНИЙ БЕРЕМЕННОСТИ

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Введение. Гормональная система «витамин D/рецепторы витамина D» участвует в регуляции многочисленных физиологических процессов. Недостаточность или дефицит витамина D ассоциируются с рядом различных заболеваний, в том числе с осложнениями беременности.

Целью исследования стало определение статуса витамина D и его влияния на течение гестационного процесса у женщин южного региона Украины.

Материалы и методы. Обследовано 459 женщин, из которых 318 (69,3%) составили основную группу, 141 (30,7%) – группу сравнения. Кроме стандартных общеклинических обследований, методом иммуноферментного анализа на анализаторе COBAS Integra 400 Plus (Roche Diagnostics, Швейцария) в крови определяли уровень витамина D.

Результаты и обсуждение. В основной группе у 49,9% из 459 беременных уровень витамина D был недостаточным (25,45 \pm 4,63 нг/мл), у 19,4% соответствовал дефициту (15,28 \pm 4,78 нг/мл). В группе сравнения концентрация витамина D составила 43,38 \pm 9,67 нг/мл ($p < 0,01$). Достоверно более частыми осложнениями беременности в основной группе были угроза прерывания (45,6% против 9,9%; $F = 0,00001$; $p < 0,01$), преэклампсия (13,5% против 2,8%; $F = 0,0093$; $p < 0,05$), плацентарная дисфункция (32% против 7%; $F = 0,00001$; $p < 0,01$), вагинальный дисбиоз (64,4% против 18,4%; $F = 0,00001$; $p < 0,01$), анемия беременных (43,7% против 20,6%; $F = 0,0008$; $p < 0,01$) и признаки воспаления околоплодных оболочек (38,3% против 13,4%). Синдром внутриутробной задержки роста диагностирован у 9% женщин основной группы, в группе сравнения не отмечалось ни одного случая.

Выводы. У 70% беременных в Одесском регионе имеется недостаточность или дефицит витамина D. Течение беременности характеризуется достоверно большей частотой преэклампсии (в 4,8 раза чаще), плацентарной дисфункцией (в 4,5 раза чаще), угрозой невынашивания (в 4,6 раза чаще), внутриутробным инфицированием (в 2,8 раза чаще), гестационной анемией (в 2,5 раза чаще). Дальнейшие исследования возможности профилактики осложнений гестационного процесса путем коррекции статуса витамина D позволяют говорить о перспективности данного направления.

Ключевые слова: гормон витамин D, рецепторы витамина D, осложнения беременности, преэклампсия, плацентарная дисфункция.

РОЛЬ ГОРМОНАЛЬНОЇ СИСТЕМИ «ВІТАМІН D/РЕЦЕПТОРИ ВІТАМІНУ D» У ФОРМУВАННІ ДЕЯКИХ УСКОПЛЕНЬ ВАГІТНОСТІ

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Вступ. Гормональна система «вітамін D/рецептори вітаміну D» бере участь в регуляції численних фізіологічних процесів. Недостатність або дефіцит вітаміну D асоціюються з низькою різниці захворювань, в тому числі з ускладненнями вагітності.

Метою дослідження було визначення статусу вітаміну D і його впливу на перебіг гестаційного процесу в жінок південного регіону України.

Матеріали та методи. Обстежено 459 жінок, з яких 318 (69,3%) склали основну групу, 141 (30,7%) – групу порівняння. Крім стандартних загальноклінічних обстежень, методом імуноферментного аналізу на аналізаторі COBAS Integra 400 Plus (Roche Diagnostics, Швейцарія) в крові визначали рівень вітаміну D.

Результати та обговорення. В основній групі у 49,9% з 459 вагітних рівень вітаміну D був недостатнім (25,45 \pm 4,63 нг/мл), у 19,4% відповідав дефіциту (15,28 \pm 4,78 нг/мл). У групі порівняння концентрація вітаміну D складала 43,38 \pm 9,67 нг/мл, ($p < 0,01$). Достовірно частішими ускладненнями вагітності в основній групі були загроза переривання (45,6% проти 9,9%; $F = 0,00001$; $p < 0,01$), преєклампсія (13,5% проти 2,8%; $F = 0,0093$; $p < 0,05$), плацентарна дисфункція (32% проти 7%; $F = 0,00001$; $p < 0,01$), вагінальний дисбіоз (64,4% проти 18,4%; $F = 0,00001$; $p < 0,01$), анемія вагітних (43,7% проти 20,6%; $F = 0,0008$; $p < 0,01$) і ознаки запалення навколоплідних оболонок (38,3% проти 13,4%). Синдром затримки внутрішньоутробного розвитку діагностовано у 9% жінок з основної групи, в групі порівняння не відзначалося жодного випадку.

Висновки. У 70% вагітних в Одеському регіоні є недостатність або дефіцит вітаміну D. Перебіг вагітності характеризується достовірно більшою частотою преєклампсії (в 4,8 рази частіше), плацентарної дисфункції (в 4,5 рази частіше), загрози невиношування (в 4,6 рази частіше), внутрішньоутробним інфекціям (в 2,8 рази частіше), гестаційної анемії (в 2,5 рази частіше). Подальші дослідження можливостей профілактики ускладнень гестаційного процесу шляхом корекції статусу вітаміну D дозволяють говорити про перспективність даного напрямку.

Ключові слова: гормон вітамін D, рецептори вітаміну D, ускладнення вагітності, преєклампсія, плацентарна дисфункція.