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About the possibility of targeted prevention of calcitriol-associated pregnancy complications at the preclinical stage

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According to recent studies, in the vitamin D deficiency state (VDD), pregnancy can be complicated and the optimal level of VD in the blood is one of the conditions for the realization of reproductive potential.
The objective: **the possibility to preventing calcitriol-associated pregnancy complications by the correcting VD deficiency at the preconception period.**
Materials and methods**. 57 women with VDD were examined. A history of all women had a pregnancy complicated by placental dysfunction (PD); 27 of them were observed from the preconception period (main group – IA) and 30 – from the 1st trimester of pregnancy (comparison group – IB). The VD status by the blood level of the 25-hydroxyvitamin D by ELISA was determined.**
Women of both groups, in addition to the vitamin-mineral complex (VMC) were prescribed supplementation colecalciferol at a dose of 4.000 IU per day. Pregnant women of both groups received VMCs up to 16 weeks. After optimizing the level (3–4 months), women continued to take VD at a dose of 2.000 IU per day throughout pregnancy.
Results**. At the initial study, the VD level was 15.72±2.59 ng/ml in IA and 16.1±1.99 ng/ml in IB group (U=883; p>0.05); after treatment increased to 38.31±3.29 ng/ml and 36.13±2.99 ng/ml (U=900; p>0.05). In group IA, the course of pregnancy was characterized by a lower frequency of complications: PD was diagnosed in 22.2% in group IA and 50% in group IB (F=0.0001; p<0.01); fetal distress in 3.7% and 10% (F=0.16; p<0.05): signs of amnionitis – in 18.5% and 33.3% (F=0.035; p<0,05); placental hypertrophy or hypotrophy – in 7.4% and 36.7% (F=0.00001; p<0.01), preeclampsia in 3.7% and 6.7% of women (F=0,54; p<0.05). The frequency of cesarean section in the comparison group was significantly higher (40% VS 25.9%, F=0.034; p<0.05).**
Conclusions**. During pregnancy, which occurred in conditions of VDD, the frequency of some pregnancy complications, including preeclampsia, the threat of miscarriage, placental dysfunction was in 2–4 times higher than in women with optimized VD status. One of the directions of the individual management plan for women with a negative obstetric history can be the determination of the level of VD in the blood and correction of the VDD at the preconception period. This approach is a pathogenetically substantiated and promising direction for the prevention of some pregnancy complications and improvement of perinatal outcomes.**
Keywords: *pregnancy, deficiency vitamin D, placental dysfunction, preconception period.*

Про можливість таргетної профілактики кальцитріол-асоційованих ускладнень вагітності на доклінічному етапі

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За даними досліджень останніх років, в умовах дефіциту вітаміну D (VDD) вагітність може супроводжуватися різними ускладненнями і оптимальний рівень VD в крові є одним з умов для реалізації репродуктивного потенціалу.
Мета дослідження: вивчення можливості профілактики кальцитріол-асоційованих ускладнень вагітності шляхом корекції недостатності або дефіциту VD на догравідарному етапі.
Матеріали та методи. До групи увійшли 57 повторнороділей з VDD. В анамнезі у всіх була вагітність, ускладнена плацентарною дисфункцією (ПД); з них 27 спостерігалися з догравідарного етапу (основна група – ІА) і 30 – з І триместра вагітності (група порівняння – ІВ).
Методом ІФА за рівнем у крові 25-гідроксивітамину D визначали VD-статус.
Жінкам обох груп на додаток до вітамінно-мінеральному комплексу (ВМК) був призначений холекальциферол у дозі 4000 МО на добу. ВМК жінки обох груп отримували до 16 тиж гестації. Після оптимізації рівня (3–4 міс) VD був призначений у дозі 2000 МО на добу протягом всієї вагітності.
Результати. При первинному зверненні рівень VD становив 15,72±2,59 нг/мл у ІА і 16,1±1,99 нг/мл у ІВ групах (U=883; p>0,05); після лікування збільшився до 38,31±3,29 нг/мл і 36,13±2,99 нг/мл відповідно (U=900; p>0,05). У ІА групі ускладнення вагітності відзначали достовірно рідше: ПД діагностовано у 22,2% у ІА і у 50% у ІВ групах (F=0,0001; p<0,01); дистрес плода – у 3,7% і у 10% відповідно (F=0,16; p<0,05): ознаки амніоніту – у 18,5% і у 33,3% (F=0,035; p<0,05); гіпер- або гіпотрофію плаценти – у 7,4% і у 36,7% (F=0,00001; p<0,01), прееклампсію – у 3,7% і у 6,7% жінок відповідно (F=0,54; p<0,05). Достовірно вищою була частота кесарева розтину у групі порівняння – 40% проти 25,9% в основній групі (F=0,034; p<0,05).
Заключення. При вагітності, що настала в умовах VD-дефіцитного стану, частота деяких ускладнень вагітності, у тому числі прееклампсії, загрози передчасного переривання, плацентарної дисфункції, була у 2–4 рази вище, ніж у жінок з оптимізованим VD-статусом. Одним з напрямків індивідуального плану ведення жінок з обтяженим акушерським анамнезом може бути визначення у сироватці крові рівня вітаміну D і корекція вітамін D-дефіцитного статусу на етапі догравідарної підготовки. Це є патогенетично обгрунтованим і перспективним напрямком профілактики деяких ускладнень вагітності і поліпшення перинатальних наслідків.
Ключові слова: *вагітність, дефіцит вітаміну D, плацентарна дисфункція, догравідарна підготовка.*

О возможности таргетной профилактики кальцитриол-ассоциированных осложнений беременности на доклиническом этапе

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По данным исследований последних лет, в условиях дефицита витамина D (VDD) беременность может сопровождаться различными осложнениями и оптимальный уровень VD в крови является одним из условий для реализации репродуктивного потенциала.

Цель исследования: изучение возможности профилактики кальцитриол-ассоциированных осложнений беременности путем коррекции недостаточности или дефицита VD на догравидарном этапе.
Материалы и методы. В группу вошли 57 повторнородящих женщин с VDD. В анамнезе у всех была беременность, осложненная плацентарной дисфункцией (ПД); из них 27 наблюдались с догравидарного этапа (основная группа – IA) и 30 – с I триместра беременности (группа сравнения – IB).
Методом ИФА по уровню в крови 25-гидроксивитамина D определяли VD-статус.
Женщинам обеих групп в дополнение к витаминно-минеральному комплексу (ВМК) был назначен холекальциферол в дозе 4000 МЕ в сутки. ВМК женщины обеих групп получали до 16 нед гестации. После оптимизации уровня (3–4 мес) VD был назначен в дозе 2000 МЕ в сутки на протяжении всей беременности.
Результаты. При первичном обращении уровень VD составил 15,72±2,59 нг/мл в IA и 16,1±1,99 нг/мл в IB группах (U=883; p>0,05); после лечения увеличился до 38,31±3,29 нг/мл и 36,13±2,99 нг/мл соответственно (U=900; p>0,05). В IA группе осложнения беременности отмечали достоверно реже: ПД диагностирована у 22,2% в IA и у 50% в IB группах (F=0,0001; p<0,01); дистресс плода – у 3,7% и у 10% соответственно (F=0,16; p<0,05): признаки амнионита – у 18,5% и у 33,3% (F=0,035; p<0,05); гипер- или гипотрофия плаценты – у 7,4% и у 36,7% (F=0,00001; p<0,01), преэклампсия – у 3,7% и у 6,7% женщин соответственно (F=0,54; p<0,05). Достоверно выше была частота кесарева сечения в группе сравнения – 40% против 25,9% в основной группе (F=0,034; p<0,05).
Заключение. При беременности, наступившей в условиях VD-дефицитного состояния, частота некоторых осложнений беременности, в том числе преэклампсии, угрозы преждевременного прерывания, плацентарной дисфункции, была в 2–4 раза выше, чем у женщин с оптимизированным VD-статусом. Одним из направлений индивидуального плана ведения женщин с отягощенным акушерским анамнезом может быть определение в сыворотке крови уровня витамина D и коррекция витамин D-дефицитного статуса на этапе догравидарной подготовки. Это является патогенетически обоснованным и перспективным направлением профилактики некоторых осложнений беременности и улучшения перинатальных исходов.
Ключевые слова: *беременность, дефицит витамина D, плацентарная дисфункция, догравидарная подготовка.*

According to recent studies, the optimal level of vitamin D (VD) in the blood is one of the conditions for the normal functioning of the ovaries and the provision of folliculogenesis, complete ovulation with oocyte production and hormonal support for the second phase of the menstrual cycle [9].

It is known that, in addition to full ovulation and sufficient gestagen levels in the luteal phase of the menstrual cycle, an endometrial condition is also important for a successful fertilization process. The presence of chronic inflammatory changes, impaired receptivity, various types of hyperplasia or «thin» edometrium, which may be associated with deficiency of calcitriol, accompanied by pathological invasion of the trophoblast, formation of a small area of uterine-placental circulation [1, 6, 3].

The knowledge that VD is involved in the formation of the implant window by regulating the expression of homeotic genes, affects the histocompatibility system of human leukocyte antigens or human tissue compatibility (Human Leukocyte Antigens – HLA), as well as data on the reduction of endometrial receptivity and endometrial receptivity inferior trophoblast invasion in conditions of insufficiency or deficiency of VD, suggest that its level in the blood of women should be optimal already at the stage of pregnancy planning [7, 8, 9, 10].

According to some studies, with a decrease in VD level of less than 30 ng/ml, and according to some sources, even 40 ng/ml, the onset of pregnancy, and even more so the formation of a full wave of trophoblast invasion raises some doubts [2, 4].

According to the guidelines for the treatment and prevention of vitamin D deficiency in the population of Central Europe [5], one to three months are required to correct vitamin D deficiency.

The objective: to investigate the possibility of preventing calcitriol-associated pregnancy complications by correcting vitamin D deficiency or deficiency at the pre-gravid stage.

MATERIALS AND METHODS

A total of 57 women were examined; the criteria for inclusion in the group were the presence of verified placental dysfunction in a previous pregnancy that ended with the birth of alive baby and the level of calcidiol (25 (OH) D) in the blood at the time of treatment and primary examination below 20 ng / ml, that is VD-deficient condition.

The criteria for exclusion from the study were the presence of severe extragenital pathology (diabetes, chronic kidney and liver disease with insufficiency), obesity, skin diseases, autoimmune disoders , patology of the thyroid and parathyroid glands.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved for all participants by the local ethics committee (LEC) of Odessa National Medical University.

After receiving informed consent for the study, the patients were divided into two groups. The main group (IA) included 27 women who applied to the stage of pregnancy planning.

VD levels in the blood were determined with the enzyme immunoassay method using 25-hydroxyvitamin D, (25-Hydroxyvitamin D, 25(OH)D), which is the best indicator for monitoring VD levels because it reflects total cholecalciferol (exogenous VD) and ergocalciferol (endogenous VD), circulates in the blood for a long time (25(OH)D half-life period is 2–3 weeks) and is not affected by PTH.

In the main group, pre-gravid preparation for the administration of the vitamin-mineral complex, which included 500 IU of colecalciferol and 800 mcg of folic acid 1 time a day, was added cholecalciferol at a daily dose of 4000 IU; the developed scheme of preparation-therapy of the patient was received within 3 months. After that, the level of VD was examined for the second time: the target value of its level was determined, as recommended, at least 30 ng/ml. Subsequently, they received a maintenance dose of VD (2000 IU cholecalciferol) throughout pregnancy; woman received a vitamin-mineral complex by the time of completion (conditionally) of the second wave of trophoblast invasion and complete anatomical and functional formation of the placenta - up to 16 weeks of pregnancy.

The second group consisted of 30 pregnant women (IB comparison group), who applied in the 1st trimester of pregnancy (up to 12 weeks), had a history of pregnancy complicated by placental dysfunction, and who had vitamin D deficiency (VDD). They were prescribed corrective therapy for VDD (4000 IU colecalciferol) from the time of diagnosis to the level of 25(OH)D in the blood of 30 ng/ml or more. In the future, they also received a maintenance dose of 2000 IU VD. All women in this group also received a vitamin-mineral complex of 1 capsule a day before the completion of the placenta formation – up to 16 weeks of pregnancy.

In patients of the main group undergoing pre-gravid preparation, the level of VD was also determined during pregnancy verification by the ultrasound method within 6–7 weeks of pregnancy with confirmed fetal heartbeat. Ultrasound was performed on the Samsung Medison UGEOWS80A (Samsung Medison CO, LTD, 2014, Korea).

In the second and third trimesters of pregnancy, the women of both groups were examined for the status of the feto-placental

complex and the condition of the fetus by ultrasound examination with feto- and placenta- metry, Doppler blood flow assessment; cardiotocography, evaluation of the biophysical profile of the fetus. Studies of the hormonal function of the placenta were done by determining the levels of human chorionic gonadotropin (HCG) and estriol. HGL and estriol levels were determined by enzyme-linked immunosorbent assay method on a Cobas Integra 400 Plus apparatus (Roche Diagnostics, Switzerland).

Statistical analysis was performed using Statistica 6.0 software from Install Shield Software Corporation (USA). To calculate the reliability of the quantitative results obtained , we used the Student's t-test for data with normal distribution and the non-parametric Mann-Whitney test for data with abnormal distribution, after determining the normality of the distribution of the data of variational series using the Shapiro-Wilk test. The reliability of the results obtained for qualitative indicators was determined using the Fisher test.

RESULTS

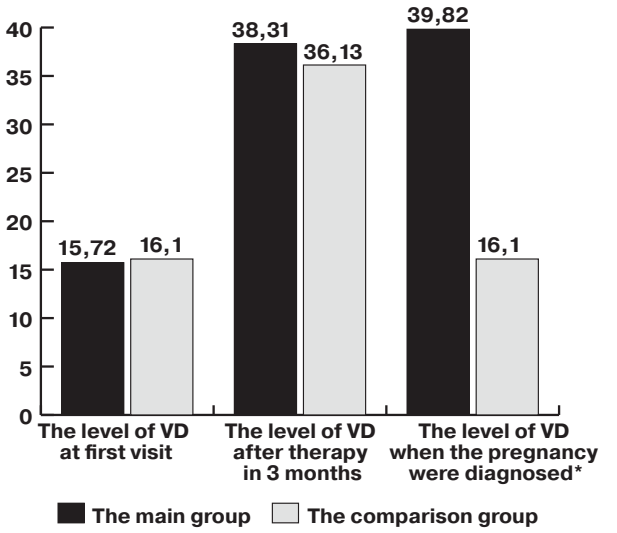
Patients of both groups were statistically homogeneous in age, anthropometric indicators, and body mass index (BMI). The age of patients ranged from 18 to 39 years and was 32.9±3.9 and 32.53±3.8 years, respectively. The weight and weight indices of women in the study groups did not deviate from the population norms, the average body weight was 61.37±5.1 and 62.7±4.22, respectively, and BMI in both groups was below 25, and was equal to 22.13±1.55 in the pre-gravidar training group, and 23.03±1.28 in the pregnant women group.

The somatic status of the patients was characterized by the following. Varicose veins of the lower extremities were detected in 22.2% of the 27 females of the main group and in 16.7% of the comparison group (F=0.21; p>0.05); vegetative-vascular dystonia was diagnosed according to groups in 11.1% and 23.3%, respectively (F=0.037; p<0.05). For other nosologies (mitral valve prolapse, NK0, goitre grade 1 with normal function of thyroid gland, chronic gastrointestinal diseases (gastritis, cholecystitis in remission), there was no significant difference between the main group and the comparison group.

According to the anamnesis, previous pregnancy was complicated by subsequent manifestations of placental dysfunction. Intrauterus fetal grow restriction (IUGR) was reported in 11.1% of the 27 main and 16.7% of the 30 women in the comparison group (F=0.31; p>0.05); 68.4% of 27 and 66.7% of 30 women had signs of inflammation of the amniotic membranes (F=1; p>0.05); disoders of Doppler metrics – 72.6% of 27 and 76.7% of 30 females (F=0.51; p>0.05). The complications of pregnancy with hypo- or hypertrophy of the placenta were raised by 38.1% of the main and 60% of women in the comparison group (F=0.19; p<0.05); about the violation of placenta in the form of its low location – 25,9% and 16,7% according to groups (F=0,17; p>0,05); about fetal distress during pregnancy or labor - 18.5% and 14.8% of women (F=0.57; p>0.05). In addition, the threat of abortion was observed in 44.4% and 56.7% of women, respectively (F=0.1; p>0.05); preeclampsia – 7.4% and 6.7%; detachment of the normally located placenta 7.4% and 6.7% of women according to groups, F = 1; p>0.05); premature rupture of the fetal membranes (PROM) – in 18.5% and 14.8% of women in the main group and comparison group, respectively (F=0.57; p>0.05).

At the time of the first examination in both groups, the level of 25(OH)D in the blood was below 20 ng/ml and was 15.72±2.59 ng/ml in the main group and 16.1±1.99 ng/ml in the comparison group (U=883; p>0.05).

After the developed complex scheme (cholecalciferol in combination with the vitamin-mineral complex) treatment (in 3 months) was determined the level of VD for the second time.



Comparative characteristics of VD levels in the blood of women in the study groups at different stages of the study
(* – differences are significant at p<0.0)

In both groups, the level of 25(OH)D incrised to the optimum level and amounted to 38.31±3.29 ng/ml in the main group and 36.13±2.99 ng/ml in the comparison group (U=900; p>0, 05).

After reaching the optimal VD level, women continued to receive cholecalciferol at a dose of 2000 U. In patients of group IA, pregnancy occurred within 1–3 months; after confirmation, according to ultrasound, pregnancy (within 6–7 weeks with a fetal heartbeat), the level of calcitriol was determined for the third time.

This indicator of the level of calcitriol in the blood of women of the main group at the stage of the first trimester was compared with the level of 25(OH)D in the blood of pregnant women of the comparison group at their first treatment in women's consultation (up to 12 weeks).

It should be noted that the level of 25(OH)D at this stage (implantation, placentation and first wave of trophoblast invasion) in the women of the main group corresponded to the level of «optimum» and was significantly higher (39.82±3.06 ng/ml), at unlike the comparison group, where all these processes took place against the background of VD deficiency – 16.1±1.99 ng/ml (U=558.5; p<0.05) (picture).

Subsequently, pregnant women of both groups received supportive VD therapy at a dose of 2000 IU until the end of pregnancy.

Analysis of pregnancy, labor and postpartum period revealed significantly more frequent complications of the gestational process and labor in the comparison group. The incidence of PD in patients who did not receive complex pre-gravid treatment was significantly higher than in the main group of women (Table). Pregnancy in all women in both groups ended with labor in time. The frequency of signs of placental dysfunction (Doppler ultrasound, IUGR) was 22.2% in the baseline and 50% in the comparison group (F=0.0001; p<0.01); fetal distress was observed in 3.7% and 10% respectively (F=0.16; p>0.05); signs of inflammation of the amniotic membranes – in 18.5% and 33.3%, respectively (F=0.035; p<0.05); placental hypertrophy or hypotrophy – 7.4% and 36.7% (F=0.00001; p<0.01), respectively, in the main and comparison groups. Preeclampsia was diagnosed in 3.7% and 6.7% of women, respectively (F=0.54; p>0.05); premature detachment of the normally located placenta – only in the comparison group of 3.3% of 30 women.

The feachures of pregnancy and labor course in women who received at the pre-gravidar stage VD (main group) and in women who did not receive it (comparison group)

The complications of pregnancy and labor	The main group, n=27		The comparison group, n=30		The reliability
	n	%	n	%	
IUGR	1	3,7	3	10	F=0,16; p>0,05
Disturbance of feto-placental blood flow	5	18,5	12	40	F=0,0018; p<0,01
Signs of inflamantion of amniotic membrane	5	18,5	10	33,33	F=0,035; p<0,05
Fetus distress	1	3,7	3	10	F=0,16; p>0,05
Hypo-, hypertrophia of placenta	2	7,4	11	36,7	F=0,00001; p<0,01
Low location of placenta	1	3,7	6	20	F=0,0008; p<0,01
Placenta preavia	0	-	5	16,67	-
Placenta detachment	0	-	1	3,3	-
Premature ripening of the placenta	1	3,7	3	10	F=0,16; p>0,05
Preeclampsia	1	3,7	2	6,7	F=0,54; p>0,05
Treatened abjrtion	6	22,2	11	36,7	F=0,0295; p<0,05
PROM	2	7,4	4	13,33	F=0,238; p>0,05
Caesarean section	7	25,9	12	40	F=0,034; p<0,05

The rate of cesarean section was significantly higher in the comparison group: 40% VS 25.9% in the main group (F=0.034; p<0.05); labor was complicated by premature rupture of the fetal membranes (PROM) 2 times higher in women in the comparison group.

CONCLUSIONS

Thus, according to the conducted researches it is possible to draw several conclusions.

Patients, who have a history of pregnancy that has been complicated by placental dysfunction are at risk of recurrence and need to develop a personalized management plan, starting with the preconception training stage.

In Vitamin-D deficiency conditions, the risk of developing certain pregnancy complications, including preeclampsia, the threat of abortion and preterm labor, placental dysfunction, etc. grows 2 - 4 times.

One of the directions for developing an individual plan for these women may be to determine in the serum the level of vitamin D, in which conditions it is possible to form complications of the gestational process and high frequency of operative delivery.

The inclusion in the program of pre-gravid preparation of cholecalciferol preparations in combination with the vitamin-mineral complex is a pathogenetically conditioned and promising approach to the prevention of complicated pregnancy and improvement of perinatal consequences.

The author declares no conflict of interest.

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REFERENCES

1. Vovk IB, Gorban NE, Borisyuk OYu. (2016). Endometrial hyperplasia (Clinical lecture). Woman's health. 5(111):10-17.
2. Eremkina AK, Mokrysheva NG, Pigarova EA, Mirnaya SS. (2018). Vitamin D: effects on the course and outcomes of pregnancy, fetal development and children's health in the postnatal period. Therapeutic archive. 10:115-127
3. Krutova VA, Kovalenko YaA. (2018). Modern ideas about the uterine form of infertility. Modern problems of science and education. http://www.science-education.ru/ru/article/view?id=27568.
4. Maltseva LI, Vasilieva EN, Denisova TG, Gerasimova LI. (2017). Availability of vitamin D and correction of its deficiency during pregnancy. Practical Medicine. 5(106):18-21.
5. Pludowski P et al. (2013). Guidelines for the treatment and prevention of vitamin D deficiency in the population of Central Europe: Recommended doses of vitamin D for healthy populations and at-risk populations. Pain. Joints. Spine. 3(11):7-12.
6. Cermisoni GC, Alteri A, Corti L, et al.(2018). Vitamin D and Endometrium: A Systematic Review of a Neglected Area of Research. Int J Mol Sci. 19(8):2320.
7. Chan SY, Susarla R. (2015). Vitamin D promotes human extravillous trophoblast invasion in vitro. Placenta. 36;4:403-409.
8. Ganguly A et al. (2018). Vitamin D, the placenta and early pregnancy: effects on trophoblast function. Journal of Endocrinology. 236;2:93-103.
9. Merhi Z et al. (2014). Vitamin D alters genes involved in follicular development and steroidogenesis in human cumulus granulosa cells. J Clin Endocrinol Metab. 99(6):1137–1145; doi: 10.1210/jc.2013-4161.
10. Palacios C, De-Regil LM, Lombardo LK, Peña-Rosas JP. (2016). Vitamin D supplementation during pregnancy: Updated meta-analysis on maternal outcomes. The Journal of Steroid Biochemistry and Molecular Biology. 164:148-155. DOI: 10.1016/j.jsbmb.2016.02.008.

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