THE EFFECT OF VITAMIN D ON PREGNANCY AND BIRTH OUTCOMES IN WOMEN WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

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Background: the relevance of undifferentiated connective tissue disease (UCTD) in obstetric and gynecological practice is associated with a high (up to 80%) prevalence of pathology among women of reproductive age and the risk of developing pathology in the pregnant woman and the newborn. ***Objective:*** to study the effect of magnesium and vitamin D in the complex therapy of pregnant women with UCTD on the course of pregnancy, childbirth, the state of women in labor and newborns. ***Methods:*** 142 women with manifestations of UCTD were analyzed during pregnancy. Depending on the treatment regimen, the patients were divided into groups: pregnant groups 1 (n = 87) received in continuous mode "Magne-B6" - 4 tablets / day (192 mg), groups 2 (n = 55) and additionally "Aquadetrim" - 1000 IU/ day. The survey was conducted according to a single scheme. ***Results:*** it was found that taking magnesium and vitamin D drugs compensates for their deficiency in the pregnant woman's body with UCTD and reduces the risk of preeclampsia (p = 0.031), fetal growth retardation syndrome (p = 0.048), contributes to a more rapid physiological adaptation of the newborn in the early postpartum period (p <0.05), its lesser morphofunctional immaturity (p = 0.030) and reduces manifestations of conjugative jaundice (p = 0.019). ***Conclusions:*** taking magnesium and vitamin D compensates for their deficiency in the body of a pregnant woman with UCTD, which reduces the risk of complications from the woman and the newborn.

Key words: undifferentiated connective tissue disease, vitamin D, magnesium, pregnancy, newborns, obstetric and perinatal complications, preeclampsia

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INTRODUCTION

At present, the group of genetically determined and clinically polymorphic pathological conditions united under the term "undifferentiated connective tissue disease" (UCTD) is becoming increasingly important in obstetric-gynecological practice. This is primarily due to its high prevalence - up to 80% among women of reproductive age and from 20 to 30% in pregnant women (1-3). Secondly, it is associated with complications of pregnancy and childbirth such as the threat of termination of pregnancy at different periods, isthmic-cervical insufficiency, gestosis, placental insufficiency and chronic intrauterine hypoxia of the fetus, premature birth, untimely discharge of amniotic fluid, uteral scar insufficiency, and postpartum hemorrhages (4,5).

It has been established that the development of the disease is based on mutations of the genes responsible for the synthesis/catabolism of the structural proteins of the connective tissue and the enzymes involved in these processes, the quantitative change in the formation of the full components of the extracellular matrix, and impared fibrillogenesis. Moreover, in recent years, there is increasing evidence of the presence of vitamin and micronutrient deficiencies in UCTD. The leading role in the development of pathology is attributed to the deficiency of Mg and vitamin D. Enhanced degradation of collagen fibers and, probably, elastin fibers, as well as polysaccharide filaments of hyaluron (3,6-9) seem to be the probable mechanisms of influence of Mg deficiency on connective tissue. American scientists in their study confirmed that a low level of vitamin D in a pregnant woman's body contributes to an

increase in the frequency of health complications in both the mother and the newborn. Children born with a vitamin D deficiency have a lower birth weight. Vitamin D deficiency during pregnancy not only disrupts the mother's skeletal system and the formation of the fetal skeleton, but also has a clear effect on the child's susceptibility to illness immediately after birth, as well as later. Nevertheless, it is noted that taking vitamin D in the form of vitamin complexes or food supplements can reduce the risk of possible complications: spontaneous abortion, premature birth, pre-eclampsia, and fetal growth retardation syndrome (10-14). Vitamin D has an integrated effect on the structure of the connective tissue: by stimulating the expression of the encoding gene of the transforming growth factor-beta, it is necessary for cell division and differentiation of osteocytes, chondrocytes, fibroblasts, and keratinocytes (15,16). At the molecular level, the effect of vitamin D is due to stimulation of prostaglandin production, an increase in intracellular pH and water content in the membrane, an influence on the metabolism of membrane phospholipids, activation of calcium channels, an increase in cytosolic and nuclear levels of ionized calcium (9,17).

Thus, the objective of this research was to study the effect of the inclusion of the magnesium and vitamin D-containing drug in the medication regimen of pregnant women with undifferentiated connective tissue disease on their course of pregnancy, childbirth, the state of new mothers and newborns.

SUBJECTS AND METHODS

The analysis of the course of pregnancy and the delivery outcomes of 142 pregnant women with manifestations of moderate severity undifferentiated connective tissue disease (UCTD) .

UCTD was diagnosed by the presence of external and visceral phenotypic symptoms of connective tissue dysplasia in women (at least 5 out of the above): hypermobility of joints, increased skin elasticity, scoliosis, congenital dislocation or dysplasia of the hip joints, spontaneous pneumothorax, nephroptosis, duplication of kidneys and / or urinary tract, increased bleeding (nasal and gingival bleeding, as well as heavy menstruation), varicose veins of the lower extremities, myopia.

To determine the UCTD severity, the criteria by T. Yu. Smolnova et al. (2003) were used. According to the author, there are distinguished:

- Minor signs (1 point): Asthenic body type or insufficient body weight, the absence of stretch marks on the skin of the anterior abdominal wall in women who had a history of childbirth, impaired refraction at the age under 40, muscular hypotonia and low manometry, flatfoot, easy bruisability, hemorrhagic tendency, hemorrhage in the puerperal period, vegetovascular dysfunctions, abnormal heart rhythm and conduction (ECG), scoliosis, kyphosis, kyphoscoliosis.
- Large signs (2 points): II-III grade flat feet, skin elastosis, hypermobility of the joints, tendency to dislocations, sprains of the joint ligaments, tendency to allergic conditions and colds, tonsillectomy, varicose disease, hemorrhoids, biliary dyskinesia, impaired evacuation, biliary tract dyskinesia, disturbed GI evacuation function.
- Severe manifestations and conditions leading to surgical interventions or having indications for them, as well as changes in anatomical relationships that led to dysfunction of organs (3 points): The threat of premature birth at 32-35 weeks, pregnancy, premature birth, fast and rapid childbirth in history with hypotonic bleeding or without it at the third stage of labor, prolapse, genitalia and hernia in relatives of the first line, hernia, splanchnoptosis, varicose veins and hemorrhoids (surgical treatment), chronic venous insufficiency with trophic disorders, habitual dislocations of the joints or dislocations of more than 2 joints, impairments of the motor function of the gastrointestinal tract, confirmed by laboratory methods (Re - logical, -scopic), diverticula, dolichosigmoid, polyvalent allergy, severe anaphylactic reactions.

The total score up to 9 corresponds to minor severity (minor UCTD); from 10 to 16 - moderate severity (moderate); from 17 and more –severe (frank UCTD).

The inclusion criteria were: age from 18 to 44 years (young age according to WHO), the presence of at least 5 phenotypic symptoms of connective tissue dysplasia in women, pregnancy on the background of UCTD, singleton pregnancy, and an informed consent to the examination.

The exclusion criteria were age over 44 years, the presence of less than 5 symptoms of connective tissue dysplasia, Marfan syndrome, incomplete osteogenesis, severe concomitant extragenital pathology that is not considered in the framework of UCTD; multiple pregnancy, refusal to sign an informed consent.

Depending on the patient's treatment regimen, the patients were divided into two groups: group 1 (main), (n=87) included pregnant women who received Magne-B6 (Sanofi, France) from the first to the end of the third trimester (12-36 weeks of gestation) in a dose of 4 tablets per day (192 mg) continuously.

The average ages of patients in the groups under study were close to each other and amounted to 25.2 ± 1.2 years in group 1 and 25.8 ± 1.2 years in group 2, respectively (p> 0.05).

The second (control) group (n=55), in addition to the magnesium drugs, received vitamin D3 (Aquadetrim, Medana Pharma, Poland) in a dose of 1000 IU/day continuously.

The women admitted of or rejected from the proposed therapy was completely dependent on the desire of patients. Some of them did not agree to take the proposed drugs (magnesium, vitamin D for personal or financial reasons).

Pregnant women were observed from the first to the end of the third trimester of pregnancy, in labor and the early postpartum period. Examination of pregnant women and women in labor was carried out according to a single scheme, including the study of general and obstetric and gynecological history, the characteristics of the course of this pregnancy, childbirth, the postpartum period of the newborn.

Analysis of the obtained data was based on the principles of evidence-based medicine. Statistical processing of the obtained data was carried out with Microsoft Excel 2007 and IBM SPSS Statistics 19 (USA). Expected arithmetic mean and standard error (M±m) were calculated. Differences between groups were evaluated by quantitative parameters using Student's t-test (p); in case of incorrect distribution of compared indicators or the number of observations in one of the groups less than 30, the Mann–Whitney u-test (pm-u) was used. Differences between groups by relative values were evaluated by the criterion χ2 (pχ2), if one of the values was less than 5, the Fisher's exact method (F) was used. Differences were considered statistically significant when the error probability (p) is less than 0.05.

RESULTS

Analysis of the incidence of pregnancy complications in women, depending on the treatment regimen, revealed (Table 1) that the group of patients, who received combination therapy with the magnesium and vitamin D-containing drug, had significantly fewer cases of pre-eclampsia (4 (7.3%) cases in the control group against 18 (20.7%) - in group 1, p=0.031) and fetal growth retardation syndrome (8 (14.5%) cases in the control group 2 against 27 (31%) in the main group (p=0.026)

Table 1.
The incidence of pregnancy complications in women with UCTD, depending on their treatment regimens

Condition	Group 1 (n=87)		Group 2 (n=55)		χ^2	p
	abs.	%	abs.	%		
Threatened abortion, first trimester	56	64.4	34	61.8	0.094	0.759
Threatened abortion, second trimester	60	69.0	39	70.9	0.060	0.806
Threatened premature birth	61	70.1	41	74.5	0.327	0.576
Isthmic-cervical insufficiency	36	41.4	27	49.1	0.812	0.368
Preeclampsia	18	20.7	4	7.3	4.633	0, 031*
Anemia of pregnancy	30	34.5	20	36.4	0.052	0.819
Chronic intrauterine fetal hypoxia	20	23.0	12	21.8	0.026	0.871
Fetal growth retardation	19	21.8	5	9.1	3.899	0.048*

Notes: * reliability - p<0.05, as compared between the groups

Premature labor was observed in 12 (13.8%) women of the main group and 8 (14.5%) of the control group (p=0.900). The analysis of the incidence of complications during labor in women suffering from UCTD, depending on their treatment regimens, revealed no significant differences between the groups, just as when comparing the incidence of postpartum complications (Table 2).

Table 2.
The incidence of labor and post-labor complications in women with UCTD, depending on their treatment regimens

Condition	Group 1 (n=87)		Group 2 (n=55)		X^2	p
	abs.	%	abs.	%		
Labor complications						
Untimely discharge of amniotic fluid	10	11.5	6	10.9	0.012	0.914
Uterine inertia	10	11.5	4	7.3	0.676	0.411
Discoordinated labor activity	8	9.2	6	10.9	0.111	0.739
Acute fetal hypoxia	9	10.3	5	9.1	0.060	0.807
Placental abruption	4	4.6	2	3.6	0.077	0.781
Postpartum complication						
Endometritis	33	37.9	17	30.9	0.728	0.393
Hematometra	6	6,9	2	3.6	0.674	0.412
Postoperative hematomas	9	10.3	5	9.1	0.060	0.807
Hypotonic bleeding	10	11.5	10	18.2	1.245	0.264
Increased blood loss in postpartum period	20	23.0	16	29.1	0.663	0.415
Mild anemia	20	23.0	10	18.2	0.467	0.494
Moderate anemia	11	12,6	7	12.7	0.000	0.988
Severe anemia	13	14,9	11	20.0	0.614	0.433

Table 3.
Average anthropometric parameters of newborns of women with UCTD depending on their treatment regimen (M±m)

Parameter	Group 1 (n=87)	Group 2 (n=55)	P
Body weight, g	3311.6 ± 544.9	3359.5± 625.5	0.655
Body height, cm	47.3± 4.4	46.6 ±5,0 cm	0.460
Chest circumference, cm	31.4 ± 2.7	32.5 ± 2.9	0.071
Head circumference, cm	32.5 ± 2.3	32.6 ± 2.3	0.801

Table 4.
Dynamics of assessment of the functional state of the newborn depending on the treatment regimens of their mothers with UCTD

Apgar score (points)	Timing of measurement									
	minute 1					minute 5				
	Group 1 (n=87)		Group 2 (n=55)		P	Group 1 (n=87)		Group 2 (n=55)		P
	Abs.	%	Abs.	%		Abs.	%	Abs.	%	
8-9 points	4	4.7	2	3.6	0.781	19	21.8	18	32.7	0.174
6-7 points	50	57.3	27	49.1	0.329	49	56.4	26	47.3	0.287
4-5 points	26	29.9	22	40.0	0.215	17	19.5	10	18.2	0.790
1-3 points	7	8.0	4	7.3	0.867	2	2.3	1	1.8	0.755

Note: p - comparison between groups 1 and 2 in terms of minutes 1 and 5

It was revealed that the average values of the anthropometric parameters of newborns at birth did not differ significantly between the groups (Table 4) and did not go beyond the average indicators of the norm.

The dynamics of the functional status of newborns on the Apgar scale 1 and 5 minutes after birth, when compared in groups at a specific point in time, had significant and statistically confirmed differences (Table 4). At the same time, newborns showed a faster adaptation to the environment, expressed in an increase in the number of newborns with a maximum score: in group 2 - 9 times (from 2 (3.6%) children during the first minute to 18 (32.7%) children by the fifth minute) than in group 1 - 4.6 times (from 4 (4.7%) children during the first minute to 19 children (21.8%) by the fifth minute of observation, respectively), $p<0.05$.

The obtained data on adaptation indicators of newborns are consistent with the analysis of complications of the early neonatal period: children born by mothers with UCTD and receiving magnesium and vitamin D during pregnancy showed signs of morphofunctional immaturity (25.4% against 42.5%) in the main group, $p = 0.030$) and the development of conjugation jaundice (27.3% against 46% in the main group, $p=0.019$)

Table 5.
The incidence of complications in the early neonatal period in newborns born by mothers with UCTD

Parameter	Group 1 (n=87)		Group 2 (n=55)		X^2	p
	abs.	%	abs.	%		
Morphofunctional immaturity	37	42.5	14	25.4	3.780	0.030*
Conjugation jaundice	40	46.0	15	27.3	5.481	0.019*
Respiratory distress syndrome	7	8.0	5	9.1	0.031	0.860
Convulsive disorder	6	6.9	6	10.9	0.632	0.427
Skin hemorrhagic syndrome	11	12.6	7	12.7	0.001	0.971

DISCUSSION

Magnesium deficiency leads to impaired metabolism of connective tissue, which is especially important for UCTD. Pregnancy itself is a condition accompanied by a deficiency of this macronutrient. Thus, the combination of UCTD and magnesium deficiency during pregnancy, aggravating each other, have an adverse effect on the course of pregnancy and its outcome (7, 8).

Vitamin D is an important prehormon that is involved in many metabolic processes. Vitamin D and 1a-hydroxylase receptors are found in the tissues of the reproductive organs, including the ovaries, uterus, placenta, testicles and pituitary gland, which confirms its role in reproductive health. The mechanisms are described, through which vitamin D deficiency in serum can increase the risk of pre-eclampsia: it is a powerful endocrine suppressor of renin biosynthesis which can prevent hypertension through suppression of the reninangiotensin system and proliferation of vascular smooth muscle cells, reduce blood insulin, improve endothelial-dependent vazodilation and inhibit anticoagulant activity. In addition, the active form of vitamin D regulates the transcription and function of genes associated with trophoblast invasion, normal implantation and angiogenesis (14,16,18). The relationship between the pregnant woman and the fetus leads to the fact that the maternal deficiency of vitamin D during pregnancy creates a deficient state in the child, beginning with the period of intrauterine development. Drug compensation of this condition in a pregnant woman reduces the risk of complications from both the new mother and the newborn (9,17).

Thus, the obtained results of treatment of pregnant women with undifferentiated connective tissue disease confirmed the data on the effectiveness of combination therapy with magnesium and vitamin D: a lower percentage of preeclampsia (18.2% against

34.5% in the control group, p=0.035) and fetal growth retardation (14.5% against 31%, respectively, p=0.026) were detected. Moreover, analysis of the condition of the newborns of these mothers revealed faster physiological adaptation in the early postpartum period (an increase in the number of children with Apgar scores of 8–9 from 3.6% during the first minute to 32.7% by the fifth minute against 4.7% and 21.8%, respectively, in the control group, p<0.05; they showed significantly less signs of morphofunctional immaturity (25.4% against 42.5% in the main group, p=0.030) and the development of conjugation jaundice (27.3% against 46% in the main group, p=0.019).

CONCLUSION

Thus, oral administration of magnesium and vitamin D drugs throughout pregnancy compensates for their deficiency in pregnant women with undifferentiated connective tissue disease, which reduces the risk of preeclampsia (18.2% against 34.5% in the control group, p=0.035) and fetal growth retardation syndrome (14.5% against 31%, respectively, p=0.026). Moreover, analysis of the condition of the newborns of these mothers revealed faster physiological adaptation in the early postpartum period (an increase in the number of children with Apgar scores of 8-9 from 3.6% during the first minute to 32.7% by the fifth minute against 4.7% and 21.8%, respectively, in the control group, p<0.05; they showed significantly less signs of morphofunctional immaturity (25.4% against 42.5% in the main group, p=0.030) and the development of conjugation jaundice (27.3% against 46% in the main group, p=0.019).

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S A Ž E T A K

UTJECAJ VITAMINA D TIJEKOM TRUDNOĆE I POROĐAJA ŽENA S RAZLIČITOM BOLESTI VEZIVNOG TKIVA

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Pozadina: Važnost nediferencirane bolesti vezivnog tkiva (UCTD) u opstetričkoj i ginekološkoj praksi povezana je s visokom (do 80%) učestalošću patologije među ženama u reproduktivnoj dobi i rizikom od razvoja patologije kod trudnica i novorođenčadi. ***Cilj:*** Proučiti utjecaj magnezija i vitamina D u kompleksnoj terapiji trudnica s UCTD-om na tijek trudnoće, porođaja, stanja trudnica i novorođenčadi. ***Metode:*** Analizirane su 142 žene s manifestacijama UCTD tijekom trudnoće. Ovisno o režimu liječenja ispitanice su podijeljene u skupine: trudnice skupine 1 (n = 87) primljene u kontinuiranom načinu rada "Magne-B6" - 4 tablete/dan (192 mg), trudnice skupine 2 (n = 55) i dodatno Aquadetrim "- 1000 IU/dan. Istraživanje je provedeno prema jedinstvenoj shemi. ***Rezultati:*** Utvrđeno je da uzimanje lijekova s magnezijem i vitaminom D kompenzira njihov nedostatak u tijelu trudnice s UCTD i smanjuje rizik od preeklampsije (p = 0,031) kao i sindrom zastoja rasta fetusa (p = 0,048), doprinosi bržoj fiziološkoj prilagodbi novorođenčeta u ranom postporođajnom razdoblju (p <0,05), manja je morfofunkcijska nezrelost (p = 0,030) i smanjene su manifestacije konjugacijske žutice (p = 0,019). ***Zaključak:*** Uzimanje magnezija i vitamina D kompenzira njihov nedostatak u tijelu trudnice s UCTD-om što smanjuje rizik od komplikacija kod žene i novorođenčeta.

Ključne riječi: nediferencirana bolest vezivnog tkiva, vitamin D, magnezij, trudnoća, novorođenčad, opstetrijske i perinatalne komplikacije, preeklampsija