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Manasova G.S.
Odessa National Medical University, Department of Obstetrics and Gynecology №2, MD, professor. Address: 65009, Odessa, St. Marshal Govorov, 28; tel .: +3 8050 502 70 58; e- mail: gulsymmanasova@gmail.com. ORCID: Manasova G.S .: http: orcid.org/0000-0002-1600-5215.
Zelinsky A.A.
Odessa National Medical University, Head of the Department of Obstetrics and Gynecology №2, MD, professor. Address: 65009, Odessa, St. Marshal Govorov, 28; tel .: +3 80 66 220 20 59.
Didenkul N.V.
Odessa National Medical University, Head of the Department of Obstetrics and Gynecology №2, graduate student. Address: 65009, Odessa, St. Marshal Govorov, 28; tel .: +3 8 093 844 6766; e - mail: didenkunatalya@gmail.com
Zhovtenko O.V.
Odessa National Medical Unuversity, Department of Obstetrics and Gynecology 2, PhD, Assistent of Professor. Adress:65009, Odessa, St. Marshal Govorov,28; tel.: +3 8 097 9411686; e-mail: olesia.zhovtenko@gmail.com
Kuzmin N.V.
PI "Maternity Hospital No. 5", resident doctor of the 2nd obstetric department. Address: 65009, Odessa, St. Marshal Govorov, 28; tel .: +3 8097 686 82 36; e - mail: tata.od.us@ukr.net.

FAULTY PLACENTATION AND ATTITUDE IN PREGNANT WOMEN WITH PLACENTAL DYSFUNCTION: REVISITED OF CALCITIROL POSSIBLE ROLE IN THE FORMATION OF PATHOLOGY

Abstract. *Placental dysfunction (PD) is one of the reasons that determine the rates of perinatal morbidity and mortality. Recent studies have demonstrated a certain effect of vitamin D (VD) on PD development. Objective. To determine the possible relationship between VD status and faulty placentation and its structural features in PD pregnant women. Materials and methods. 56 pregnant women with PD and 40 healthy women with a physiological course of pregnancy were examined. The level of VD in the patients' blood was determined by enzyme-linked immunoassay (EIA) method; placenta's attitude and its structural and functional features were determined by ultrasound, Dopplerometric methods. Results. 66.07% of PD pregnant women under examination had placenta's abnormal/faulty attitude or its structural changes. Normal placenta's attitude without structural organometric changes was noted only in 33.93% of PD pregnant women (OR=192,18 95%; CI 25.68 – 1438.38; χ2 = 98.51; p<0,001). 35.13% of pregnant women with abnormal placentation had calcitriol level corresponding to suboptimal (20-30 ng / ml) or deficient status with VD significantly lower average blood level compared to the control group (31.40 ± 8.6 VS 43.54 ng / ml; p ≤ 0.05). Conclusions. Calcitriol may have some influence on the formation, development and functioning of utero-placental-fetal blood circulation. Further researches to obtain information on the role of VD in this process are needed.*
Key words. *Placental dysfunction, vitamin D, abnormal attitude of the placenta.*

Introduction. Placental dysfunction (PD) develops as a result of initial violation of utero-placental-fetal system formation or its affect under development and functioning as an independent anatomical object. PD development depends on a woman performance status, her anthropometric data, life style peculiarities, bad health habits presence, etc. Each pregnant woman body features, the acceptability of additional screening tests, and each medical establishment possibilities affect the curability of PD [1].

According to the literature data, placenta's abnormal, faulty attitude is a serious cause of PD development with a high risk of maternal and perinatal losses. Occurrence of *placenta previa* varies from 0.3 to 1.04 % that of low placentation up to 9.1% [2, 3].

Recent studies show that PD and fetal growth retardation (FGD) may be associated with vitamin D deficiency (VD), which leads to abnormal apoptosis of the placental trophoblast and impaired cell cycle differentiation [4].

Inadequate trophoblast invasion, inadequate remodeling of uterine arterioles, decreased proliferation and increased cytotrophoblast apoptosis, impaired vascular invasion due to VD deficiency or deficiency are associated with

placental insufficiency [5, 6, 7, 8].

The objective: to determine the possible effect of vitamin D status on the faulty placentation and attitude in pregnant women with placental dysfunction.

Materials and methods. 56 pregnant women with PD aged (29.21 ± 4.3 y. o.) were examined; the comparison group consisted of 40 conditionally healthy patients with a physiological course of pregnancy, aged (30.35 ± 3.12 y. o.; p> 0.05). According to anthropometric data, the way of life both groups were uniformed. Body mass index (BMI) in the main group patients corresponded to (22.2 ± 1.7) conventional units (c.u.), and in the control group - (22.8 ± 1.93) c.u., (p > 0.05).

General clinical examination of the patients, special clinical and laboratory examinations to assess the state of the fetus and utero-placental-fetal circulation (ultrasound, Dopplerometric, hormonal, and other methods) were carried out in accordance with the requirements of regulatory documents in the prescribed periods of pregnancy and / or according to medical grounds.

The placenta anatomical attitude, its structural and functional features were determined by ultrasound, Doppler methods.

The VD level in the blood of the patients was determined by enzyme immunoassay. 25 hydroxycalciferol - (25 (OH) D) - is the main metabolite of calcitriol, reflects its total concentration in D3 (cholecalciferol) and D2 (ergocalciferol) forms, was quantified.

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

All the patients gave informed consent to conduct surveys.

Results and discussion.

It is known that the causes of anomalies of the placenta attitude and implantation may be due to the somatic state of the pregnant woman or the peculiarities of the ovum. According to the the data of literature, low placentation is diagnosed in almost 10%, *placenta previa* in 0.3 - 1.04% of the total number of births.

According to our data, PD pregnant women anamnesis was characterized by a significantly higher frequency of extragenital pathology (Table 1).

Table 1.

Features of the somatic status of pregnant women with placental dysfunction and healthy pregnant women

Nosoform	Main group		Control group		significance
	Abs. number	%	Abs. number	%	
Vegetative-vascular dystonia	7	12	0	0	F=0.003; p<0.05
Prolapse of the mitral valve, NK-0	6	10.7	1	2.5	F=0.0092; p<0.05
Chronic gastritis	4	7.14	0	0	F = 0.007; p <0.05;
Chronic cholecystotis	1	1.79	2	5	F = 0.44; p> 0.05
Chronic pyelinephritis	21	37.5	6	15	F = 0.0006; p <0.05;
Chronic tonsillitis	9	16.07	2	5	F = 0.0096; p <0.05;
Varicose veins of low limbs	4	7.14	0	0	F = 0.007; p <0.05;
Diffused goiter	4	7.14	1	2.5	F = 0.085; p> 0.05
Mild myopia	7	12.5	0	0	F = 0.0003; p <0.05;

The frequency of cardiovascular diseases in the main group pregnant women was 23.12%, which is 10 times more than in the control group (2.5%; F = 0.0003; p <0.05); diseases of the gastrointestinal tract were diagnosed in 7.14% vs 0% (F = 0.007; p <0.05) women of the main and control groups. A significantly higher rate of inflammatory diseases in the patients of the main group, including urinary system (37.5% vs. 15%; F = 0.0006; p <0.05) and nasopharyngeal diseases (16.07% against 5%; F = 0.0096; p <0.05) cannot but be noted. Thyroid gland diseases were 3 times more often diagnosed in women with PD (10.71% vs. 2.5%; F = 0.0092; p <0.05). Varicose veins of the lower extremities were detected in 7.14% of pregnant women of the main group (F = 0.007; p <0.05).

It should be noted that some pregnant women had polypathia of GIT tract and kidneys, CVS and kidneys, etc.

In the presence of extragenital pathology, a set of inflammatory, metabolic, circulatory changes in the microvasculature, including directly in the forming utero-placental circle of the blood circulation, is accompanied by general pathological processes in the form of attitude anomalies, impaired maturation of the villous space, dystrophic and other changes in the placenta with a violation of its compensatory adaptive capabilities.

Reproductive and gynecological history of pregnant women of both groups was characterized by a number of features (Table 2).

Table 2

Features of gynecological and obstetric history of the pregnant women under examination

Indicator	Main group		Control group		Significance
	Abs. Number	%	Abs. Number	%	
Primipara (first pregnancy)	40	71.43	22	55.00	F=0.028;p<0.05
Primipara (consecutive pregnancy - m/a, s/a)	7	12.5	2	5.0	F=0.045; p<0.05
Multipara	16	28.57	18	45	F=0.028;p<0.05
Cervical erosion	15	26.79	2	5.00	F=0.00003;p<0.05
Scleropolycystic ovarian syndrome	2	3.57	0	0	F=0.012;p<0.05
Primary infertility	12	21.43	4	10.00	F= 0.049;p<0.05
Uterine hypoplasia	2	3.57	0	0	F=0.012;p<0.05
Saddle uterus	2	3.57	0	0	F=0.012;p<0.05
Uterine fibroids	6	10.71	0	0	F=0.002;p<0.05
Asherman's syndrome	2	3.57	0	0	F=0.012;p<0.05
Chronic salpingoophoritis	6	10.71	1	2.5	F=0.003; p<0.05
Premature delivery in the history	9	16.07	1	2.5	F=0.0014;p<0.05
The presence of a scar on the uterus after a cesarean section	8	14.29	5	12.5	F=0.83; p>0.05

Primiparous patients (first-pregnant) accounted for 71.43% of all women in the main group, in the control group - 55.00% (F = 0.028; p <0.05); multiparous women constituted respectively 28.57% and 45% (F = 0.028; p <0.05). It is known that the likelihood of formation of placental dysfunction during the first pregnancy and first birth is higher, which is explained by the insufficiently developed adaptive capabilities of the uteroplacental system [9].

28.5% primiparas of the main group patients indicated a miscarriage in history, which is 10 times more than in the control group — 2.5% (F = 0.0008; p <0.05).

Cervical erosion in patients of the main group was diagnosed in 26.57% of cases, while in the control group (5.00%) it was 5 times less (F = 0.00003; p <0.05); the presence of scleropolycystic ovarian syndrome (SPOS) and Asherman's syndrome was indicated in 3.57% of patients, uterine fibroids had 10.71% of patients with PD. There were no such patients in the control group. Inflammatory diseases of the uterus appendages were significantly more frequently observed in the main group (10.71% vs. 2.5%; F = 0.03; p <0.05). In addition, in 21.43% of the main group patients and in 10.00% of the control group ones, pregnancy occurred after the treatment of primary infertility of various origins (F = 0.049; p <0.05). It should be noted that in 7.14% of PD patients there were failures of uterus development such as a saddle-shaped uterus and its pre-pregnancy hypoplasia, which can act as independent factors in the pathology of implantation, placentation and fetalization.

*In 14.29% and in 12.50% of women in the main and control groups there was a scar on the uterus after the previous cesarean section (F = 0.83; p> 0.05). The lack of significant differences in the frequency of cesarean section can probably be explained by the fact that the number of multiparous patients in the control group is 1.5 times more than in the main group.

Features of reproductive and gynecological

history of PD pregnant women indicate the presence of certain conditions for its formation. Thus, a high incidence of miscarriage, inflammatory diseases of the pelvic organs, underlying diseases of the uterus and directly of the uterus can contribute to the development of anatomical and functional changes in the endometrium, with a subsequent effect on the processes of implantation of the ovum and placentation [10]. An additional risk factor for the formation of an "inconsistent implantation window" and pathological placentation can be hormonal disorders due to the presence of SPOS [11, 12].

When analyzing the characteristics of the placenta anatomical location in the uterus, it was found that the most frequent abnormality is low placentation, which was detected in every fourth pregnant woman with PD (26.79%) (Fig. 1).

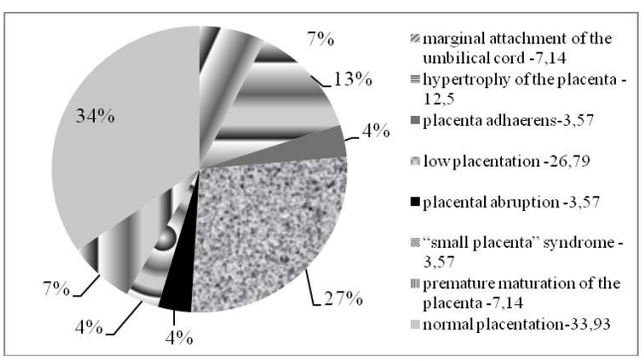

Fig. 1. The frequency of faulty placentation and attitude and placenta the structural changes in pregnant women with placental dysfunction

In the control group, the placenta abnormally low attitude was observed in 5.00% of the womwn under observation at the term of 12 weeks, which is 3.5 times less (F = 0.00003; p <0.05) than in the main group.

The index of marginal placentation in PD pregnant women which was detected in 7.14% of cases, also testifies to a violation of the placenta migration capacity and unfinished to the terms of labours migration.

It is known that with the faulty placentation there is so-called "migration phenomenon", which can be accompanied by bleeding of varying intensity [13]. The migration process may initiate the threat of abortion, premature birth, placental insufficiency, placental abruption and other perinatal complications. Atypical placentation is a risk factor of PD early formation [2].

In 12.5% of PD pregnant women, hypertrophy of the placenta was diagnosed, in 3.57% - a small in area placenta and in 7.14% of them a premature placenta maturation was observed.

The placenta structural changes described as well as its impairments can be regarded as clinical markers of placentogenesis incompleteness and predictors of PD [14] development. Placental morphogenesis depends on the development of the utero-placental blood circulation system as a whole: placental hypertrophy and "small placenta" syndrome is characterized by association with placental insufficiency and delayed fetal development [15, 16].

Impaired implantation of the ovum and the degree of trophoblast invasion, followed by abnormal placenta tight attitude and its premature detachment was observed in 7.14% of PD pregnant women.

According to the data of literature, the pathological invasion of interstitial cytotrophoblast in early pregnancy without adequate expansion and opening of the spiral arteries (the first wave of invasion) and insufficient migration of intravascular cytotrophoblast cells into the walls of the myometrial segments of the spiral arteries (the second wave of invasion) is a condition for the formation of local (initially) endothelial dysfunction and placental insufficiency [17, 18].

Normal anatomical attitude of the placenta without any structural ogranometric changes was observed only in 33.93% of PD pregnant women. Overall, 66.07% of them had various abnormalities of placentation or structural changes in the placenta (OR = 192.18; 95% CI; 25.68-11438.38; $\chi 2 = 98.51$; $p < 0.001$) .

In the study of vitamin D status, it was established that out of 37 pregnant women (66.07%) with pathology of the placentation and its structural changes, in 13 (35.13%) calcitriol level corresponds to suboptimal (20-30 ng / ml) or deficit status (less than 20 ng / ml), (Fig.2).

The mean VD level in PD patients was significantly lower than in the control group (31.40 ± 8.6 vs 43.54 ng / ml; $p \leq 0.05$).

The results obtained are consistent with the literature data on the involvement of the VD / VDR system in providing a quality "implant window" and the processes of trophoblast

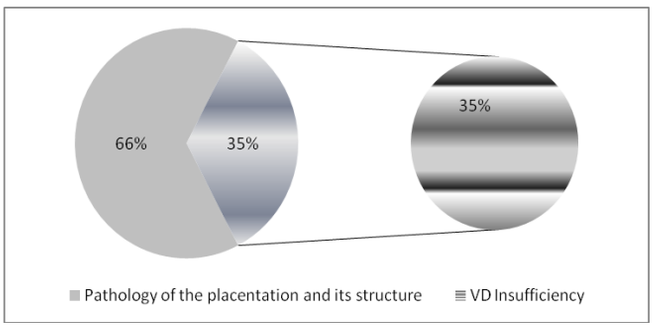

Fig. 2. The frequency of vitamin D deficiency in pregnant women with the placenta faulty attitude and its structural changes

invasion into the uterus [19]. The probability of pregnancy loss in the first trimester in women with low VD levels is 2 times higher than in women with optimal levels of VD in the blood [20].

According to the latest data, the effect of vitamin D on angiogenesis can be both stimulating and overwhelming: it depends on the types and condition of the cells, the activity of angiogenesis, and the chemokines involved in this process. It is assumed that VD contributes to the resolution of pro- and antiangiogenesis [21].

Conclusions. In pregnant women with placental dysfunction, a general somatic history is burdened with a significantly higher frequency of extragenital morbidity (cardiovascular system — 10 times, kidney disease — 2.5 times, gastrointestinal diseases — 1.78 times, inflammatory diseases of the nasopharynx - 3 times, diseases thyroid gland - 3 times). Varicose veins of the lower extremities were detected only in 7.14% of pregnant women of the main group.

The gynecological history in pregnant women with placental dysfunction is characterized by a significantly higher incidence of inflammatory and dyshormonal diseases.

The frequency of vitamin D-deficiency status in pregnant women with placental dysfunction is 1.9 times greater than in pregnant women with a physiological course of the gestational process (RR = 1.42; CI 95%; 1.08 -1.87, $p \leq 0.05$).

More than 2/3 of pregnant women with placental dysfunction revealed faulty placentation and attitude or placenta's structural changes. Normal anatomical localization of the placenta without any structural ogranometric changes was observed only in 1/3 of PD pregnant women.

In 35.13% of placental dysfunction pregnant women and faulty placentation and attitude, the level of VD corresponds to a deficient or suboptimal status which requires its additional administration.

This suggests that calcitriol may have a certain effect on the formation, development and functioning of the utero- placental-fetal circulation and its insufficient level, probably accompanied by pathological changes in a complex system of compensatory-adaptive mechanisms. Further research is needed to obtain information on the role of VD in these physiological and pathological processes.

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