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OTIGINAL ARTICLE

Primary Placental Dysfunction Development Features in Women at High Risk and the Prognostic Value of Biochemical Screening

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KEYWORDS

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ABSTRACT: Pregnancy forms an integral part of lives of more than half of the female population. During this period, there is greater need to take care of woman's health and the health of her child, so the relevance of this study is conditioned by the necessity of taking a more responsible approach to pregnancy, especially in the early stages. Since the disease detected at an early stage is easier to control and to intervene with minimal threat to the lives of woman and her child in case of threat. As part of the project, 30 pregnant women with hyperandrogenism (HA) and 30 pregnant women with uncomplicated pregnancy were examined. The main selection criterion is the presence of deviations according to the results of the first biochemical screening in pregnant women of the study group and placental dysfunction (PD) according to histological examination. Placental lactogen, estriol, progesterone, fibrin degradation products (FDPs), soluble fibrin monomer complexes (SFMCs) were determined in pregnant women of the "risk group" for the frequency of PD at 16-18 and 20-24 weeks of gestation. Decreased levels of progesterone more than 2 times, placental lactogen 3 times, estriol 1.5 times compared with the data in physiological pregnancy is an indication for a comprehensive examination of pregnant women in the absence of clinical symptoms of PD. Based on this result, it was determined that pregnant women at risk who are prone to abnormalities need to re-tested and examined two to three times more often than other women.

INTRODUCTION

Placental dysfunction (PD) is a key issue in obstetrics, neonatology and pathological anatomy of the ante- and perinatal period diseases [1, 2]. Therapeutic measures for the prevention and treatment of PD, conventionally carried out in the middle or end of the second trimester of pregnancy, when the placentation and formation of secondary placental villi is completed, are not always effective, therefore the relevance of early diagnosis and prognosis of PD is increased. In modern conditions, the role of endocrinopathies of various geneses, including hyperandrogenism (HA), in the development of PD has been increasing [3-6]. Adequate development of the maternal-placental-foetal system depends on the implantation of the fertilised egg, cytotrophoblastic invasion, as well as the subsequent transformation of the spiral arteries [3]. In the pathogenesis of PD, the leading role is played by the decreased uteroplacental and foetal-placental circulation, delayed development of cotyledons [2, 3 and 5]. The main reason for the decrease in blood flow in the intervillous space is the absence or insufficient gestational transformation of the myometrial segments of the spiral arteries [4, 6].

During pregnancy, the concentrations of human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) synthesised by syncytiotrophoblast and extravillous cytotrophoblast may indicate latent defects in implantation and early placental formation that appear as the following complications (foetal growth cessation, miscarriage up to 22 weeks, premature birth up to 37 weeks, gestosis), and not only indicate the presence

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of foetal malformations [3, 7 and 8]. Some scientists believe that PAPP-A simulates the maternal immune response and is one of the factors that ensure the development of the placenta [3, 7]. Diagnosis of foetal growth cessation risk in early pregnancy in women with low levels of PAPP-A was historically the first clinical application of the determination of PAPP-A in serum, proposed in the early 1980s [4, 8]. Decreased levels of free hCG may indicate a risk of miscarriage, abortion [2]. The position of the chorion and placenta in the uterine cavity is of particular importance in the development of PD [9]. With an abnormal chorionic/placental position, changes in haemodynamics in the maternal-placental-foetal system, haemostasis system, hormonal function of the fetoplacental complex lead in 61.8% of cases to the development of PD. The severity and frequency of it are directly dependent on the variant of the abnormal chorionic/placental position. The greatest risk of PD exists in the incomplete process of placental migration – its low position [3, 10].

In abnormal position of the chorion/placenta in the lower parts of the uterus the thin wall of the lower uterine segment does not provide necessary conditions for sufficient vascularisation of a placental bed, full gestational transformation of myometrial segments of spiral arteries that in turn leads to decrease in blood supply of the placenta and the foetus. Hypoxemia, which develops as a result, activates the uterine contractile activity, is of a protective nature in the initial stages, promoting the movement of blood in the intervillous space. At the same time, long-term increase in the tone and excitability of the uterus can lead to myometrial ischemia, disruption of the chorion-decidual membrane connections, and to uteroplacental blood flow pathology and chorionic detachment in the future. These changes also reduce the compensatory-adaptive capabilities of the maternal-placental-foetal system; promote the development of primary placental dysfunction (PD), slow down the growth and development of the foetus, causing a complicated course of pregnancy and childbirth [11-14].

MATERIALS AND METHODS

The purpose of the study was to assess the morpho-functional state of uteroplacental blood flow during the formation of primary placental dysfunction in women at risk (hyperandrogenism, abnormal chorionic/placental position). The study of the prognostic value of PAPP-A and human chorionic gonadotropin (hCG) concentrations in relation to the occurrence of primary PD in pregnant women with hyperandrogenism. To assess the endocrine function of the placenta in pregnant women at risk as a basis for the diagnosis of pathological conditions of the foetus. To assess the blood flow in the spiral arteries during physiological pregnancy in the course of the first trimester of pregnancy. To determine the state of blood flow in the spiral arteries of the central and peripheral part of the placenta in the course of pregnancy in women with PD, on the basis of which to develop new diagnostic and prognostic criteria for the foetus and new-born, as well as morphometry of endometrial spiral arteries in the first trimester in normal and abnormal pregnancy affected by PD. Morphological and immunohistochemical parameters of the state of hormonal-protein metabolism in the trophoblast of the chorionic villi in early pregnancy with low chorionic position [15].

The study group A (30 patients) included pregnant women with subtle forms of HA, diagnosed in the first trimester of pregnancy. The diagnosis of HA was confirmed both clinically and in the laboratory: an increase in the concentration of testosterone, androstenedione, dehydroepiandrostenedione sulphate (DHEA-S). The study group B included 25 women with low placentation. The main selection criterion was the presence of PD according to histological examination. The control group consisted of 30 pregnant women with no pregnancy complications, complicated gynaecological and obstetric history. Data from the results of the first biochemical screening are presented. Comprehensive examination of patients included general clinical, biochemical, enzyme-linked immunosorbent assay, ultrasound, Doppler, cardiotocographic methods.

Pregnant women "at risk" is a category of patients who have complications during pregnancy due to disruption of the vital functions of a woman's body. There is also a notion that the “risk group” is a group that includes patients with a high probability of developing foetal pathology due to disorders of certain functions of the female body, they are prone to certain diseases that can harm foetal growth and general maternal health.

Regarding the occurrence of placental dysfunction at 16-18, 20-24 weeks of pregnancy, a study of reproductive hormones was conducted in pregnant women "at risk", according to conventional methods: placental lactogen (PL), estriol (E3), progesterone (P), fibrin degradation products (FDPs), soluble fibrin monomer complexes (SFMCs). That is why doctors should be especially responsible for women who are prone to develop abnormalities. All pregnant women "at risk" should be examined by the chief doctor of the women's clinic, if medically required, the mother gets additional consultation from respective specialists. This is done to address the possibility of prolonging the pregnancy [16].

Morphological features of the chorion and decidual tissue at its low position and immunohistochemical methods have effectively studied trophoblast hormones such as HG, placental lactogen, and pregnancy specific trophoblastic beta-1 glycoprotein (SP1), which play an important role in the formation of structures and functions.

RESULTS AND DISCUSSION

According to our results, the main complication of the first half of pregnancy in women with HA is the threatened abortion (100%), and in 46.7% of cases there was cervical insufficiency, partial chorionic separation (100%) in a short time, premature rupture of membranes – 46.7%, abnormal labour – 66.7%. According to Doppler velocimetry results, uterine and (or) fetoplacental blood flow disorders were present in 30 (100%) pregnant women of the study group, and only 1 (3.0%) of the control group ($p<0.05$). Foetal distress was diagnosed in 73.3±5.2% and IUGR in 43.3±5.3% ($p<0.001$). According to our data, 86.6±4.0% of children from mothers of the study group were born with low birth weight, and 46.7±4.9% were also premature, in the control group the corresponding figures are as follows – 6.7±4.6% and 6.7±4.6% ($p<0.001$). When statistically processing the results of the first biochemical screening, the authors of the study found that the level of hCG in the blood averaged 24,198±0.5 mIU ml^{-1} in the study group, which is 36.7% lower than this value in the control. The level of PAPP-A in the serum of pregnant women with HA was 1,960±0.9 mIU ml^{-1}, which is 45.8% less than in the control group.

Pregnant women with HA and a combination of medical history data (miscarriage at 6-7 weeks of pregnancy, undeveloped pregnancy, habitual miscarriage, antenatal foetal death in the anamnesis, prolonged risk of miscarriage, partial chorionic separation, premature birth, both previous and in this pregnancy), and the presence of deviations of the first biochemical screening, in which at 16-18 weeks of pregnancy a decrease in the level of P (34.58±0.48 nmol l^{-1} vs. 76.18±0.41; $p<0.0001$), PL (1.13±0.02 mg l^{-1} vs. 3.48±0.04 mg l^{-1}, $p<0.0001$) is determined compared with the control group by 50% or more and a decrease in the level of estriol by 1.5 times (12.36±0.15 nmol l^{-1} vs. 18.38±0.33 nmol l^{-1}; $p<0.0001$), form a group at increased risk of PD development. At 20-24 weeks, pregnant women in this group undergo a comprehensive examination. In addition to the state of hormonal function of the placenta, a study of the regulation system of the blood physical state, placento- and foetometry, Doppler velocimetry. At a decrease in the level of P (46.27±2.28 vs. 109.7±2.1 nmol l^{-1}; $p<0.0001$), PL (3.42±0.08 vs. 5.67±0.05 mg l^{-1}; $p<0.0001$), E3 (28.06±0.39 vs. 86.23±0.24 nmol l^{-1}; $p<0.0001$) by 1.5-2 times and more than the normative values; an increase in the level of fibrin degradation products (8.20±0.90 vs. 0.78±0.20 μg ml^{-1}; $p<0.0001$) and soluble fibrin monomer complexes (36.57±2.13 vs. 8.46±1.61 μg ml^{-1}; $p<0.0001$) by more than 2 times, hospitalisation is indicated for pregnant women to an institution of the third accreditation level for additional examination, development of tactics and delivery time. During a physiological course of pregnancy, a decrease in vascular resistance in uterine arteries (UtAs) occurs at 12-13 and 20-22 weeks; in the spiral arteries – at 8-10 and 13-14 weeks of pregnancy, which reflects the completion of trophoblast invasion and gestational changes of the spiral arteries (degeneration of the muscular layer, endothelial cell hypertrophy, fibrinoid necrosis of the terminal parts), henceforth blood flow in these vessels remains stable until the end of pregnancy [17, 18]. The increase in vascular resistance in SA that occurs earlier than in UtAs is a prognostically unfavourable sign in relation to the development of disorders of the maternal-placental-foetal functional

system [19]. In 25 pregnant women of the control group in the first trimester of pregnancy, Doppler examination revealed the progressive development of low-resistance blood flow in the basin of the uterine arteries. This can be confirmed by the literature [20], which shows that normal blood flow in UtAs in the first trimester of pregnancy is characterised by a decrease in peripheral resistance indices (SDR, PI, RI).

The state of blood flow in the uterine arteries at 5-8 weeks of pregnancy in 25 women with low placentation was studied (Table 1).

Table 1. Doppler study values of uterine arteries blood flow at 5-8 weeks of pregnancy in women with low placentation, (M±m).

	Values	Study group (n=25)	Control group (n=25)
Right uterine artery	SDR	10.02±0.9	10.12±0.9
	RI	0.98±0.06	0.94±0.05
	PI	1.65±0.14	1.36±0.13
	PSV, cm sec^{-1}	38.9±1.6*	49.1±2.1
	EDV, cm sec^{-1}	6.0±0.7	7.5±0.8
	ADV, cm sec^{-1}	5.6±0.6*	7.7±0.8
	TAMAX, cm sec^{-1}	13.9±1.0*	18.9±1.3
Left uterine artery	SDR	10.95±1.0	9.87±0.9
	RI	1.2±0.08*	0.95±0.06
	PI	1.8±0.18*	1.33±0.13
	PSV, cm sec^{-1}	44.9±1.7	50.2±2.2
	EDV, cm sec^{-1}	5.4±0.6*	7.4±0.7
	ADV, cm sec^{-1}	5.3±0.6*	7.2±0.7
	TAMAX, cm sec^{-1}	15.6±1.1	18.1±1.2

The data obtained in our studies show that changes in hemodynamic values (SDR, RI, PI) in the left UtA in women with low chorionic position at 5-8 weeks of pregnancy were more pronounced compared with the control group. Probably, this can be explained by the predominant position of the villous chorion on the left side of the uterus, which contributed to the registration of higher values of resistance indices.

The analysis of the blood flow velocities in UtAs showed that in the right UtA pulse systolic velocity and time-averaged maximum velocity in the study group was significantly lower compared to the control group ($p<0.05$). In the left UtA at low placentation there is a significant increase in vascular resistance (RI, PI), as well as a significant decrease in blood flow velocities (EDV, ADV) in comparison with pregnant women with a normal chorionic position. This may be considered an unfavourable prognostic sign due to a decrease in blood flow to the SA and further into the intervillous space.

The authors of this study also investigated similar Doppler parameters at 9-12 weeks of pregnancy in both physiological pregnancy and low chorionic position. Data on studies of uterine arteries blood flow are shown in Table 2.

Table 2. Doppler study values of uterine arteries blood flow at 9-12 weeks of pregnancy in women with low placentation, (M±m)

	Values	Study group (n=25)	Control group (n=25)
Right uterine artery	SDR	8.2±0.8*	6.1±0.6
	RI	0.95±0.06*	0.79±0.05
	PI	1.8±0.17*	1.3±0.15
	PSV, cm sec^{-1}	62.3±2.9*	76.2±3.1
	EDV, cm sec^{-1}	14.1±0.9*	18.9±1.2
	ADV, cm sec^{-1}	14.5±0.9*	18.5±1.2
	TAMAX, cm sec^{-1}	30.9±1.4*	38.8±1.5
Left uterine artery	SDR	7.5±0.7*	5.8±0.5
	RI	0.93±0.07*	0.75±0.04
	PI	1.7±0.18*	1.2±0.14
	PSV, cm sec^{-1}	59.8±2.3*	73.1±2.8
	EDV, cm sec^{-1}	13.6±0.9	15.8±1.0
	ADV, cm sec^{-1}	10.9±0.8*	16.2±1.1
	TAMAX, cm sec^{-1}	24.3±1.3*	32.5±1.5

Based on the data shown in Table 3, highly resistant blood flow is maintained in the right and left UtA at 9-12 weeks of pregnancy with low placentation. The study of blood flow in both UtAs revealed a significant increase in resistance (SDR, IR, PI) and a significant decrease in blood flow velocities (PSV, EDV, ADV, TAMAX, cm sec^{-1}) in pregnant women of the study group compared with similar values in pregnant women of the control group ($p<0.05$). According to numerous researchers, the PI of the uterine arteries reflects the degree of invasion of the trophoblast into the spiral arteries [21]. Thus, the increase of this value may indicate the beginning of primary PD development in pregnant women with abnormal chorionic/placental position. Thus, the detected blood flow disturbances in the uterine artery progress in the course of pregnancy, which leads to PD aggravation and an increase in the level of pregnancy complications. All patients also underwent three-dimensional ultrasound to obtain a three-dimensional image of the chorion. Volumetric reconstruction of chorionic blood flow was performed in the program VOCAL (Virtual Organ Computer-Aided Analysis) with the construction of a histogram of the vascular component in a given volume of chorionic tissue. This allowed performing automatic calculation of chorionic volume and volumetric blood flow with determination of vascularisation index (VI) and blood flow index (FI).

Table 3. Indices values of vascular resistance in the spiral arteries of the central part of the placenta in pregnant women with various forms of placental dysfunction

Group, RI	6-8 weeks	9-12 weeks	16-18 weeks	20-24 weeks
Control group, n=30	0.32+0.01	0.31+0.01	0.31±0.01	0.31±0.01
Study group, n=55	0.43+0.01 **x**	0.39+0.01 **x**	0.38+0.02 **x**	0.39+0.02 **x**

Note: **x** is the reliability coefficient of the value difference in comparison with the 1st group ($p<0.05$).

The results of the study allowed identifying regularities of the chorion vascular component development in physiological pregnancy. According to the time periods of chorion structural development, the data were analysed separately during villi formation (up to 8 weeks) and during cotyledons formation (up to 12 weeks). Three-dimensional reconstruction of the chorion was obtained in 100% of pregnant women in the first trimester of pregnancy, which allowed analysing the histograms. With the development of pregnancy from 5 to 12 weeks, there is a gradual increase in the volume of the chorion from 1.7 to 72.9 cm^3 in pregnant women with normal chorionic position. At 5-8 weeks of pregnancy in the control group, the average chorionic volume was 11.35±1.1 cm^3 (Figure 1). In pregnant women with a normal chorionic position, at 9-12 weeks, this figure corresponds to 69.20±4.5 cm^3. These numbers, of course, indicate the nature of chorionic tree development and the activity of cotyledon formation.

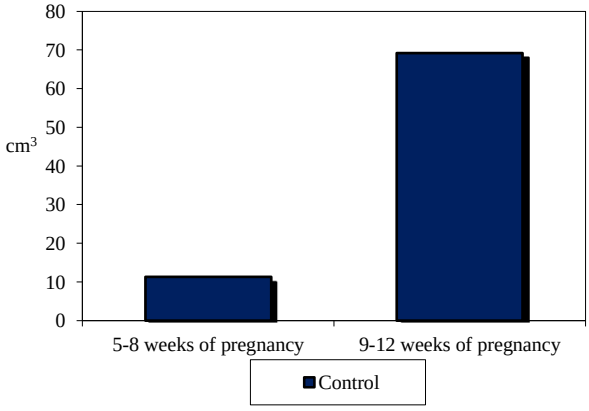

Figure 1. Chorionic volume at 5-12 weeks of pregnancy.

The data obtained on changes in chorionic volume in the course of pregnancy indicate that pregnant women with the corresponding pathology should be classified as "at high risk" of PD. The data obtained in our study showed

that in the right uterine artery SDR (7.1±3.5) and RI (0.8±0.1), PI (2.2±0.5) were slightly lower than in the left one – SDR (7.3±3.6) and RI (0.7±0.2), PI (2.1±0.8). The uterine arteries pulsatility index reflects the degree of trophoblast invasion in the spiral artery and can be used as a prognostic indicator of the pathological course of pregnancy. Values of systolic blood flow velocity, both peak (PSV 53.1±26.3) and average diastolic velocity (ADV 9.3±7.3) were significantly higher at seven weeks of pregnancy in the right uterine artery compared to the left (respectively PSV – 51.2±18.5 and ADV – 10.1±5.7). This trend was observed at 12 weeks of pregnancy as well. In the spiral arteries, all resistance indices (SDR, RI, PI) in the course of the first trimester of pregnancy decreased slightly. The blood flow velocities curves of the spiral arteries have a relatively high diastolic blood flow velocity, which increases in the course of the first trimester. In turn, the indices of spiral arteries vascular resistance are lower compared to the uterine ones. Evaluation of the nature of hemodynamic curves showed that the parameters of peripheral vascular resistance fluctuated in the course of the first trimester of pregnancy, respectively, SDR – 2.57-2.7, PI – 0.55-0.6, RI – 0.96-1.2. The curves of blood flow velocity, namely PSV and EDV, increased slightly, the indicators of average diastolic velocity (ADV) and time-averaged maximum velocity (TAMAX) were significantly unchanged.

As a result of the analysis of the received data it was established that the greatest intensity of haemodynamics in the pool of uterine arteries at 11–12 weeks of pregnancy was registered in the group of patients with favourable consequences of pregnancy. Thus, the systolic-diastolic ratio in the right and left uterine arteries in these patients was 1.9±0.3 and 2.1±0.35, respectively, significantly higher (by 1.6-1.9 times). Pulsating arterioid-like blood flow was not detected in any of the pregnant study groups. The obtained data allowed concluding that the physiological course of pregnancy is most characterised by the lack of blood flow registration in the intervillous space in the first trimester of pregnancy. As a study result, the authors established that based on dynamic Doppler velocimetry of pregnant women from the comparison group the resistance index for SA in the central part of the placenta in the course of pregnancy did not decrease, and the blood flow condition in the peripheral placenta was different. The RI values in this part of the placenta were higher than in the central part at all times of the examination. In the course of pregnancy, the intensity of blood flow in the peripheral part of the placenta increased, which was expressed in decreased RI.

Therefore, our results show that in the control group at all times the blood flow intensity was higher in the central part of the placenta than in the peripheral part, and its percentage difference was maximum at 20-24 weeks ($p<0.01$) and decreased during pregnancy by almost three times (18.8% to 6.5%) due to improved haemodynamics of peripheral areas of the placenta.

Besides, in women of the study group SA RI of the central part of the placenta was higher at all times of the examination relative to the control group ($p<0.01$). In the peripheral part of the placenta, the indicators of vascular resistance were also higher than in the control group at all times except at 16-18 weeks. Over time the resistance index decreased till 16-18 weeks in all areas of the placenta. In women of the study group there was a slight percentage difference in blood flow intensity in the SA of the central and peripheral parts of the placenta at 9-18 weeks of pregnancy (2.3-2.6%), and at 20-24 weeks the hemodynamic status was the same in all parts of the placenta. In contrast to the control group, in women of the study group at 9-12 weeks the SA IR of the peripheral part of the placenta was lower than the central part ($p>0.05$) (Table 4).

Table 4. Values of vascular resistance indices in the spiral arteries of the peripheral placenta in pregnant women with various forms of placental dysfunction

Group, RI	6-8 weeks	9-12 weeks	16-18 weeks	20-24 weeks
Control group, n=30	0.38+0.01	0.35+0.01	0.35+0.01	0.33+0.01
Study group, n=55	0.42+0.01 **x**	0.40+0.02 **x**	0.39+0.02 **x**	0.39+0.01 **x**

Note: **x** is the reliability coefficient of the value difference in comparison with the 1st group ($p<0.05$).

Analysis of haemodynamics in the spiral arteries in pregnant women with intrauterine growth restriction (IUGR) revealed that highly resistant blood flow (highly resistant with regard to the control group) was characteristic for these women at all times of the examination. In the course of pregnancy, RI decreased till 9-12 weeks only in the central departments ($p<0.01$). It was diagnosed that at 16-18 weeks of pregnancy there was a slight percentage difference in the intensity of blood flow to different parts of the placenta in pregnant women with IUGR: it was increased by 2.3% in the peripheral part of the placenta. The ratio of SA RI of the peripheral part of the placenta to the central part was less than one at 16-18 weeks in 14% of pregnant women in the control group and in 79.2% of the study group, and in 87.8% of pregnant women with IUGR. These data allowed establishing the diagnostic parameter for placental dysfunction, which is determined at 9-12 weeks of pregnancy in relation to the resistance indices of the spiral arteries of the peripheral part of the placenta to the central one, and at a value less than 1.0 of which PD was diagnosed, which in the course of pregnancy is manifested in the form of sub- or decompensated form.

Analysis of the RI average values of in SA showed that in pregnant women of the study group the indices were higher than in the control group ($p<0.01$) and in the course of pregnancy they decreased in the study group till 16-18 weeks ($p<0.05$), and in pregnant women with IUGR did not have a significant decrease. Complete transformation of the spiral arteries of the endometrium during pregnancy contributes to its successful course and development of the foetus. It is accompanied by a loss of vasomotor control, decreased local arterial resistance, dilation of vascular lumen and provides an increase in uteroplacental blood flow, adequate to the growing needs of the foetus. Violation of this process leads to the development of pregnancy complications, including preeclampsia, intrauterine growth restriction, and spontaneous abortion. The transformation of the arteries of the placental bed has several stages and is associated with trophoblast invasion. In the first trimester of pregnancy, the spiral arteries of the endometrium are first transformed, and later the changes spread to deeper segments of blood vessels. In a normal pregnancy, 96% of the spiral arteries of the endometrium undergo rearranging. The prevalence of vascular transformation varies in different arteries and even in different parts of the same vessel. At the same time in the central part of the placental bed in which trophoblastic invasion is most intensive, changes in vessels are most expressed.

Gestational transformation of spiral arteries in normal pregnancy. In the study of the uterine-placental area in Group 1, it was found that the invasion of the internal cytotrophoblast into the endometrial segments of the spiral arteries during the first trimester increases ($p<0.001$), reaching a pronounced: 5-6 weeks – 1.6±0.2, 7-8 weeks – 2.1±0.2, 9-10 weeks – 2.5±0.1. The degree of fibrinoid deposition during the first trimester increases: 5-6 weeks – 1.3±0.1, 7-8 weeks – 2.0±0.1, 9-10 weeks – 2.9±0.1 ($p<0.001$), and leads to total replacement of muscle-elastic fibres of the wall spiral arteries. As a result, by the end of the first trimester, the lumen of the endometrial segments of the spiral arteries becomes significantly expanded, and the gestational transformation of the spiral arteries in a normal pregnancy is complete. When the placenta is immature, the internal and interstitial invasion of the cytotrophoblast is decreased. The decrease in intravascular invasion is confirmed by the lower frequency of cytotrophoblastic plugs in the lumen of the spiral arteries, which in relative immaturity of the placenta are found on average 2.3 times less often than in normal pregnancy, and in pathological immaturity of the placenta are not detected. The degree of gestational transformation of the spiral arteries in the first trimester with relative immaturity of the placenta averages 42.0%, and with pathological immaturity of the placenta – only 16.2% (Table 5).

Table 5. Degree of gestational rearrangement of the spiral arteries in placental immaturity (%)

Placental immaturity	Gestational age			Total
	5-6 weeks	7-8 weeks	9-10 weeks	
Relative	36.1	43.3	45.2	42.0
Pathological	16.4	16.5	15.6	16.2

Comparison of the obtained data with the assessment of the curves of blood flow velocities in the uterine arteries revealed some patterns. In the absence of blood flow in the interveolar space, the absolute values of the systolic-diastolic ratio in the right and left uterine arteries were significantly lower – 1.8±0.1 and 2.0±0.2, respectively, than in cases with venous blood flow – 2.6±0.2 and 2.9±0.2, respectively. These data suggest that the absence of blood flow in the intervillous space and the presence of its venous type are variants of the norm in the uncomplicated course of pregnancy. The obtained data suggests that the physiological course of pregnancy is most characterised by the lack of registration of blood flow in the intervillous space in the first trimester of pregnancy.

The appearance of venous-type blood flow, registered in some patients with physiological course and favourable consequences of pregnancy, may indicate the inclusion of certain compensatory mechanisms in response to the decrease in the intensity of uteroplacental haemodynamics. The pulsating arterioid wave of blood flow velocity curves corresponds to the "fountain-like" blood regurgitation from the spiral arteries lumen, which, in our opinion, indicates incomplete gestational adjustment and preservation of unstriated muscle fibres in the walls of these vessels. Thus, placental immaturity in the first trimester is a significant percentage of unrecognised pathological processes: based on medical abortions, it is detected in 34.8% of cases, including relative immaturity – 23.0%, pathological immaturity – 11.8%.

Analysis of histometric parameters of placentas from women with hyperandrogenism showed the presence of a low level of adaptive reactions at the tissue level and did not confirm their accelerated development. The revealed histological changes were characterised by severe variants of pathological immaturity of placental tissue: 43.8% dominated by intermediate immature villi, 15.6% – intermediate differentiated villi, 40.6% – chaotic sclerotic villi, which indicates a lag in the development of villous tree at 6-10 weeks in comparison with normal rate of gestation. Chaotically sclerotic villi were dominated by active fibroblasts and collagen fibres, which compressed the capillaries from the outside until they were completely closed.

The thickness of the syncytiotrophoblast in the study group of pregnant women ranged from 5.3-6.0 μm (control group – 3.8-4.3 μm), and the thickness of the placental barrier – 9.9-11.8 μm (control group – 8.2-9.7). A sharp thickening of the placental barrier (fibroblasts, collagen fibres) leads to a significant deterioration of the diffusion properties of the placenta. The high amount of intervillous fibrinoid (from 4 to 8%, while in the control group – 2-4%) in the placenta causes the adhesion of villi and the separation of blood of the mother and foetus. Therefore, morphological studies of the placenta confirmed the presence of severe, irreversible changes in the diffusion capacity of the placenta, indicating the presence of primary PD. In medical abortions performed in early pregnancy, histological sections clearly show that in the group of pregnant women with low chorionic position (the study group) there is a decrease in the intensity of trophoblast invasion in the uterine-placental area. This manifests itself primarily by the reduction in the number of trophoblast cells, in particular the cytotrophoblast. In addition, there is a low presence of invasive trophoblast in the uterine SA compared with the control group.

To assess the maturation degree of the chorionic tree according to the classification of villous formations [21] in the modification [22], the following variants of villous chorionic formations were found in histological specimens: mesenchymal, embryonic, intermediate immature, stem "early", trophoblastic and villous processes. Analysing the percentage of different types of villous formations in the gestation period of 5-8 weeks in pregnant women with low and normal chorionic position, one can see that no significant changes are observed in this period of pregnancy. Only in pregnant women of the study group there is a decrease in the percentage of trophoblastic and villous processes in comparison with the control group, respectively, 10.4±0.22 and 11.6±0.45 (Table 6, Figures 2, 3).

Reduced number of trophoblastic and villous processes. Haematoxylin-eosin. Vol.3.5x. Circ.10x. The number of trophoblastic and villous processes prevails. Haematoxylin-eosin. Vol.3.5x. Circ.10x.

Figure 2. Abortion, study group, 7 weeks of pregnancy.

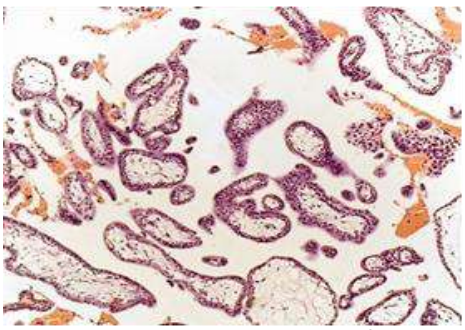

Figure 3. Abortion, control group, 7 weeks of pregnancy.

Table 6. Ratio of different types of villous formations in the gestation period of 5-8 weeks (M±m)

Types of villous formations	Control group (n=25)	Study group (n=25)
Stem "early" villi	1.5±0.12	1.7±0.18
Trophoblastic and villous processes	11.6±0.45	10.4±0.22*
Mesenchymal villi	20.3±0.61	20.6±0.23
Embryonic villi	60.0±1.39	60.5±1.58
Intermediate immature villi	6.6±0.70	6.8±0.86

Note: * statistically significant differences of the main observation group compared with the control group ($p<0.05$)

11 weeks of pregnancy. Intermediate immature and embryonic villi predominate, the percentage of villous and trophoblastic processes is reduced. Haematoxylin-eosin. Vol.3.5x. Circ.10x.

Intermediate immature and embryonic villi, villous and trophoblastic processes prevail. Haematoxylin-eosin. Vol.3.5x. Circ.10x.

During the gestation period of 9-12 weeks, there are characteristic changes in the villous chorion in the study group, which are as follows: when calculating the ratio of different types of villous formations, a decrease in the percentage of trophoblastic and villous processes is found. Evidently (Table 7, Figures 4, 5), in pregnant women with low chorionic position, trophoblastic and villous processes are 6.2±0.27, compared with the control group, where this Figure is 32.6% higher. This indicates a decrease in the rate of new villi formation and may explain the small mass of the placenta, which is observed later in women who carried to term. Analysis of the data indicates that the first probable changes in the villous formations appear only at 9-12 weeks of pregnancy.

Table 7. The ratio of different types of villous formations in the gestation period of 9-12 weeks (M±m)

Types of villous formations	Control group (n=25)	Study group (n=25)
Stem "early" villi	8.7±0.40	8.9±0.39
Trophoblastic and villous processes	9.0±0.42	6.2±0.27*
Mesenchymal villi	1.9±0.18	2.6±0.16
Embryonic villi	29.4±1.86	30.2±1.51
Intermediate immature villi	50.6±1.98	52.1±1.73

Note: * statistically significant differences of the main observation group compared with the control group ($p<0.05$)

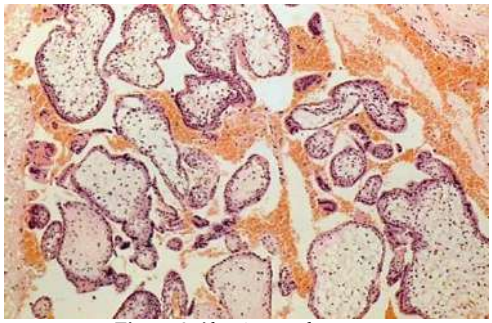

Figure 4. Abortion, study group.

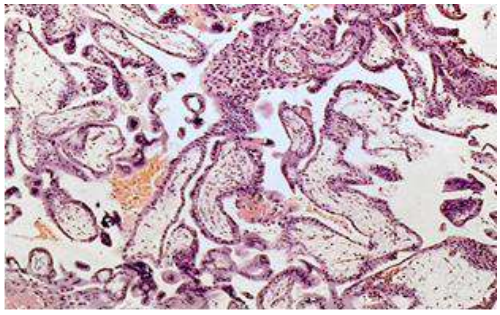

Figure 5. Abortion, control group, 10 weeks of pregnancy.

Locations of HG hormones, placental lactogen and pregnancy specific protein SP1 were identified by the use of immunohistochemical method by the brown colour, which was small and granular and among all structures of chorionic villi was found only in the cytotrophoblast and syncytiotrophoblast. According to Tables 6 and 7, starting from 5-8 weeks of pregnancy with low chorionic position, the concentration of hCG begins to slightly decrease by 2.2%, placental lactogen by 2.8% and SP1 protein by 2.7% compared with the control group ($p<0.05$).

The level of protein oxidative modification in the

trophoblast cytoplasm of the chorionic villi was also determined. No significant difference in the value of the R/B ratio in pregnant women of the study and control groups was found (Table 8).

Table 8. Some immunohistochemical and histochemical parameters of the hormonal-protein metabolism state in the chorionic trophoblast at the gestational age of 5-8 weeks (M±m) cond. units of optical density

Parameters	Control group (n=25)	Study group (n=25)
Optical density of specific immunohistochemical staining for chorionic gonadotropin	0.319±0.0021	0.312±0.0018*
Optical density of specific immunohistochemical staining for placental lactogen	0.294±0.0024	0.286±0.0023*
Optical density of specific immunohistochemical staining for SP1 protein	0.305±0.0022	0.297±0.0021*
R/B ratio (test for protein oxidative modification)	0.98±0.12	1.01±0.13

Note: * statistically significant difference between parameters in the observation groups ($p <0.05$)

Analysis of the data presented in Table 7 indicates that at 9-12 weeks of pregnancy there are more significant hormonal and protein changes in the chorionic trophoblast: the amount of hCG in the study group is significantly reduced by 6.3% compared with the control group, placental lactogen – by 10.9%, SP1 – by 5.4% ($p<0.05$), which indicates the beginning of primary PD development. It should be noted that there is a significant ($p<0.05$) increase in the value of the R/B ratio in pregnant women at 9-12 weeks of pregnancy with low chorionic position, which is confirmed by an increase in the above parameters. Thus, characteristic changes are observed in the villous chorion in pregnant women with low chorion position, which are as follows: a decrease in the percentage of trophoblastic and villous processes, the thickness of the trophoblastic cover of the chorionic villi, and a decrease in the intensity of trophoblastic invasion in the uterine-placental area. In the early stages of pregnancy (5-12 weeks) with low chorionic attachment in the lower segment of the uterus, the beginning of the primary PD development is noted, which is confirmed by a significant decrease in the concentration of HG,

placental lactogen and trophoblastic β-glycoprotein in the chorionic trophoblast.

CONCLUSIONS

Therefore, for prognosis and early diagnosis of primary PD, the authors of this study have developed an algorithm for ultrasound diagnosis and prediction of primary PD in early gestation in high-risk pregnant women.

1. Pregnant women with low placentation, hyperandrogenism in early pregnancy are recommended to be included in the high-risk group for the development of primary placental dysfunction. Disruption of steroidogenesis reduces the hormonal activity of the placenta, probably in connection with reduced activity of growth factors involved in placentation and remodelling of the spiral arteries and leads to the development of primary placental dysfunction.
2. Detection of abnormalities is the basis for a comprehensive examination of pregnant women with HA in the absence of clinical symptoms of PD, and the right time and method of delivery will reduce the level of perinatal losses and complications.
3. The diagnostic parameter of placental dysfunction, which is determined at 9-12 weeks of pregnancy in relation to the resistance indices of the spiral arteries of the peripheral part of the placenta to the central part, and at a value less than 1.0 of which PD was diagnosed, which in the course of pregnancy manifests itself in sub- or decompensated form.
4. During the first ultrasound screening, to determine the ratio of the resistance indices of the spiral arteries of the peripheral part of the placenta to the central, and if its value is less than 1.0 to diagnose placental dysfunction, which in the course of pregnancy manifests itself in sub- or decompensated form ($p<0.01$).
5. If there are symptoms that may indicate the development of implantation and placentation pathology, the state of haemodynamics should be re-evaluated with ultrasound (if an increase in RI, decrease in PI, decrease in SDR is found in the spiral arteries, even without symptoms of early termination of pregnancy, medications that improve blood flow in the spiral and uterine arteries should be prescribed).

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None.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Zelinsky A.A., Karaush E.A., 2005. Perinatal Losses and Risk Factors of Obstetric and Gynecological Pathology, Kyiv: Intermed.
2. Milovanov A.P., 1999. Pathology of the Mother – Placenta – Foetus System, Moscow: Meditsina.
3. Sidelnikova V.M., 2011.Preparation and Management of Pregnancy in Women with Recurrent Miscarriage, Moscow: MEDpress-Inform.
4. Strizhakov A.N. Ignatko I.V., 2007. Loss of Pregnancy, Moscow: Medical Information Agency.
5. Azziz R., Nestler J.E., Dewailly D., 2006. Androgen Excess Disorders in Women: Polycystic Ovari Syndrome and Other Disorders, Totowa: Humana Press.
6. Beer A.E., Kwak J., 2000. Reproductive medicine program. Chicago Medical School. 11, 201-240.
7. Cuckle H.S., 2010. Monitoring quality control of nuchal translucency. Clinics in Laboratory Medicine. 30, 593-604.
8. Strukov A.I., Serov V.V., 2010. Pathological Anatomy, Moscow: Litterra.
9. Ailamazyan E.K. Obstetrics., 2005. Gynaecology, Moscow: SpetsLit.
10. Bodyazhina V.I., Zhmakin K.N., Kiryushchenkov A.P., 1986.Obstetrics, Moscow: Meditsina.
11. Mikhailenko E.T., 1982. Physiological Obstetrics, Kyiv: Vyshcha shkola.
12. Serov V.N., Strizhakov A.N., Markin S.A., 1989. Practical Obstetrics. A Guide for Doctors, Moscow: Meditsina.
13. Gavrilova L.V., 2000. On postcoital contraception. Family Planning Magazine. 1, 45-53.
14. Saidova R.A., 2000. Modern contraceptives. Family Planning Magazine. 2, 89-94.
15. Politaev G.F., 2000. Contraception: Options of choice. Family Doctor. 18, 111-117.

16. Savelyeva I.S., 1999. Influence hormonal contraceptives for the risk of developing breast cancer. Gynaecology. 1, 2-7.

17. Ketting E., Visser A.P., 1996. Contraception in the Netherlands: Low abortion rate. Family Planning Magazine. 4, 67-81.

18. Amin S.B., Sinkin R.A., Glantz J.C., 2007. Metaanalysis of the effect of antenatal indomethacin on neonatal outcomes. American Journal of Obstetrics & Gynaecology. 197, 486.

19. Mittendorf R., Dambrosia J., Pryde P.G., 2002. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. American Journal of Obstetrics & Gynaecology. 186, 1111.

20. Stika C.S., Gross G.A., Leguizamon G., 2002. A prospective randomised safety trial of celecoxib for treatment of preterm labour. American Journal of Obstetrics & Gynaecology. 187, article number 653.

21. Goldenberg R.L., 2002. The management of preterm labour. American Journal of Obstetrics & Gynaecology. 100, 1020.

22. Simhan H.N., Caritis S.N., 2007. Prevention of preterm delivery. The New England Journal of Medicine. 13, 75-81.