Angiogenic imbalance as a starting point for the development of placental dysfunction and pregnancy complications in patients with pathology of the fetal environment

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In recent years, scientific views on perinatal protection of fetus have shifted to earlier periods of pregnancy – to the I trimester, because from this stage the formation of the fetoplacental complex and laying of organs and tissues take place, which in most cases determines the further course of pregnancy.

The objective: to clarify the role of the imbalance of angiogenic growth factors as one of the pathogenetic mechanisms in the development of placental dysfunction, and to conduct a postnatal macromorphometric study of placenta and umbilical cord in women with pathology of the fetal environment.

Materials and methods. The object of the study were 80 pregnant women (the main group) with a singleton pregnancy, selected from the cohort of patients from the risk group for the development of preeclampsia and miscarriage. Among them, at 30–32 weeks of gestation oligohydramnios was diagnosed in 40 patients (the first group) and polyhydramnios – in 40 women (the second group). The control group included 30 somatically healthy pregnant women with a normal volume of amniotic fluid and a physiological course of pregnancy.

The concentrations of placental growth factor (PlGF), vascular endothelial growth factor-1 (VEGF-1), and an antiangiogenic marker of neovasculogenesis, soluble fms-like tyrosine kinase (sFlt-1), were performed at 12–16 and 28–32 weeks of pregnancy by enzyme immunoassay method. The study of the structural and functional features of the placenta and umbilical cord included sonographic and organometric methods. The variational statistical method of analysis of the obtained results was carried out using the «STATISTICA for Windows®-6.0» package.

Results. In the women of the main group in the I trimester the ultrasound signs of pathology of the embryo and extraembryonic structures were significantly more often observed: low placement of the fertilized egg (33.8 %), its deformation (27.5 %), and partial detachment of the chorion (28.5 %). At 12–16 weeks of pregnancy, a pronounced vascular imbalance was established with a 2.5-fold decrease in the concentration of PlGF in the case of oligohydramnios compared to control data, a 1.8-fold decrease in the level of free VEGF-1 (in the case of oligohydramnios), and an increased level of antiangiogenic growth factors (sFlt-1).

The postnatal examination of the placenta and umbilical cord showed that in the pregnant women of the main group a predominance of abnormal forms of placenta (16.3 %), a predominance of eccentric and marginal types of attachment of the umbilical cord (53.8 %), main and intermediate types of vascular branching (63.7 %), changes in the diameter of the umbilical cord (17.5 %), a combination of these features in a third of cases (31.3 %) were found. In the women of the main group, there was a decrease of the placental-fetal coefficient compared to the individuals of the control group, which was especially pronounced in pregnant women with oligohydramnios (up to 0.11±0.01 units compared to control data - 0.16±0.01 units).

Conclusions. In the period of 12–16 weeks of pregnancy a vascular imbalance was established at the stage of placentation in patients who were diagnosed pathology of the perinatal environment at 30–32 weeks. In particular, by oligohydramnios there is a 2.5-fold decrease in the concentration of PlGF compared to the control data, a 1.8-fold decrease in the level of VEGF-1, and an increased antiangiogenic growth factor (sFlt-1), which became a prerequisite for the development of placental dysfunction.

The results of the postnatal examination of the placenta and umbilical cord became an indirect reflection of placentation conditions. They demonstrated the predominance of abnormal forms, the predominance of the eccentric and marginal type of attachment of the umbilical cord, the main and intermediate type of vascular branching, an increased rate of umbilical cord pathology (Warton's jelly deficiency, anomalies of the umbilical cord vessels) and a decreased placental-fetal ratio in women with amniotic fluid pathology, which was it is especially pronounced with oligohydramnios.

Keywords: pregnancy, amniotic fluid index, placental dysfunction, oligohydramnios, umbilical cord pathology, angiogenesis, preeclampsia, fetal development delay, placenta and umbilical cord macromorphology.

Дисбаланс ангіогенезу як відправна точка формування плацентарної дисфункції та гестаційних ускладнень у пацієнток із патологією навколоплідного середовища

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В останні роки наукові погляди у перинатальній охороні плода змістилися до більш ранніх термінів вагітності – І триместра, тому що саме на даному етапі проходить формування фетоплацентарного комплексу, закладання органів і тканин, що у більшості випадків і визначає подальший перебіг вагітності.

Мета дослідження: уточнення значення дисбалансу ангіогенних факторів росту як одного із патогенетичних механізмів розвитку плацентарної дисфункції та проведення постнатального макроморфометричного дослідження плацент та пуповини у жінок із патологією навколоплідного середовища.

Матеріали та методи. Дослідження проводили у 80 вагітних (основна група) із одноплідною вагітністю, відібраних із когорти пацієнток з групи ризику розвитку прееклампсії та невиношування. З них у терміни 30–32 тиж гестації було верифіковано маловоддя у 40 пацієнток (перша група) та багатоводдя – у 40 жінок (друга група). До групи контролю увійшли 30 соматично здорових вагітних із нормальним об'ємом навколоплідних вод та фізіологічним перебігом вагітності. Оцінювання концентрації плацентарного фактора росту (placental growth factor – PlGF), ендотеліального фактора росту судин-1 (vascular endothelial growth factor-1 – VEGF-1), а також антиангіогенного маркера неоваскулогенезу розчинної fms-подібної тирозинкінази-1 (soluble fms-like tyrosine kinase-1 – sFlt-1) проведено у терміни 12–16 та 28–32 тиж вагітності методом імуноферментного аналізу. Дослідження структурно-функціональних особливостей плаценти та пуповини включало сонографічний та органометричний методи. Варіаційно-статистичний метод аналізу отриманих результатів проводили за допомогою пакета «STATISTICA for Windows®-6,0».

Результати. У жінок основної групи у І триместрі достовірно частіше спостерігалися ехографічні ознаки патології ембріона та екстраембріональних структур: низьке розміщення плідного яйця (33,8 %), його деформація (27,5 %) та часткове відшарування хоріона (28,5 %). У 12–16 тиж вагітності встановлено виражений судинний дисбаланс зі зниженням концентрації PlGF у випадку маловоддя у 2,5 раза проти даних контролю, зменшенням рівня вільного VEGF-1 – в 1,8 раза (у випадку маловоддя) та збільшенням рівня антиангіогенних факторів росту (sFlt-1).

Постнатальне дослідження плаценти та пуповинного канатика продемонструвало, що у вагітних основної групи виявлено домінування аномальних форм посліду (16,3 %), переважання ексцентричного та крайового типу прикріплення пуповини (53,8 %), магістрального і проміжного типу розгалуження судин (63,7 %), зміни діаметра пуповини (17,5 %), поєднання зазначених особливостей у третині випадків (31,3 %). У жінок основної групи відзначено зниження плацентарно-плодового коефіцієнта щодо осіб контрольної групи, яке було особливо виражено у вагітних із маловоддям (до 0,11±0,01 ум.од. проти даних контролю – 0,16±0,01 ум.од.).

Висновки. У терміні 12–16 тиж вагітності встановлено судинний дисбаланс на етапі плацентації у пацієнток, у яких діагностовано патологію навколоплідного середовища у 30–32 тиж. Зокрема, при маловодді відзначається зниження концентрації PlGF у 2,5 раза проти даних контролю, зменшення рівня VEGF-1 – в 1,8 раза та збільшення параметрів антиангіогенного фактора росту (sFlt-1), що стало передумовою розвитку плацентарної дисфункції.

Опосередкованим відображенням умов плацентації стали результати постнатального дослідження плаценти та пуповинного канатика. Вони продемонстрували домінування аномальних форм, переважання ексцентричного та крайового типу прикріплення пуповини, магістрального і проміжного типу розгалуження судин, зростання частки патології пуповинного канатика (дефіцит вартонових драглів, аномалії судин пуповини) та зниження плацентарно-плодового коефіцієнта у жінок із патологією навколоплідних вод, що було особливо виражено при маловодді.

Ключові слова: *вагітність, індекс амніотичної рідини, плацентарна дисфункція, маловоддя, патологія пуповини, ангіогенез, прееклампсія, затримка розвитку плода, макроморфологія плаценти та пуповини.*

In recent years, scientific views on perinatal protection of the fetus have shifted to earlier periods of pregnancy – to the first trimester, because the formation of fetoplacental complex, laying of organs and tissues take place at this stage of gestation, which in most cases determines the further course of pregnancy [1, 2, 4, 5]. The process of blastocyst implantation in the endometrium is regulated by many factors, first of all – by vascular-endothelial growth factors, the state of hemodynamics in the basal and spiral arteries of the uterus, steroid hormones of the ovaries, as well as their interaction with endometrial receptors [2, 5, 6, 11].

Taking into account the direct participation of the endothelium in the maintenance of vascular homeostasis, in the processes of vascularization during the formation of fetoplacental blood circulation, the imbalance and inferiority of various links of angiogenesis, the lack of an adequate response to the production of angiogenic factors by other sources, first of all by the trophoblast, makes a significant contribution to the understanding of the mechanisms of the formation of the placental complex at the stage placentation in patients of the risk group [8, 10, 11, 24, 27].

As scientific studies demonstrate, the realization of pathological conditions during pregnancy can contribute to the disruption of the processes of trophoblast invasion and placentation, which is associated with an imbalance in the production of angiogenic regulators – stimulators and inhibitors of vascularization [7, 8, 10, 12].

One should not exclude the fact that in the structure of the causes of perinatal morbidity and mortality, the pathology of the fetal environment is of great importance, in particular, idiopathic polyhydramnios and oligohydramnios, which are closely related to the formation of the placental complex and its function [6]. This requires the search for early criteria for the diagnosis and prognosis of placental dysfunction and its negative consequences, to which a rather large number of literary scientific reports are devoted [1, 2, 7, 17, 18, 21].

The objecticve: was to clarify the role of the imbalance of angiogenic growth factors as one of the pathoge-

netic mechanisms of the development of placental dysfunction, and to conduct a postnatal macromorphometric study of placenta and the umbilical cord in women with pathology of the fetal environment.

MATERIALS AND METHODS

The results of the study are presented as a fragment of complex research works of the Department of Obstetrics and Gynecology of Postgraduate Education of the Ivano-Frankivsk National Medical University, carried out in the family planning center of the Municipal Non-Commercial Enterprise "Ivano-Frankivsk Regional Perinatal Center of the Ivano-Frankivsk Regional Council".

At the first stage of the study, individual parameters of the angiogenic balance were evaluated in 282 patients included in the risk group for the development of miscarriage, preeclampsia, and fetal growth retardation syndrome, i.e., the main gestational complications closely related to primary placental insufficiency.

The material for the study of growth factors (GR) was the blood serum taken from the specified category of patients at 8 o'clock in the morning on an empty stomach in the 12–16 and 28–32 weeks of pregnancy, where the concentration of placental growth factor (PlGF), vascular-endothelial growth factor (VEGF-1), as well as the anti-angiogenic marker of neovasculogenesis sFlt-1 was determined by ELISA test kits from BIOSOURCE (USA) on a MULTILABEL COUNTER 1420 photometer (Denmark) according to the instructions for the kit.

At the second stage of the study, 80 pregnant women with a singleton pregnancy and a violation of the fetal environment diagnosed for the first time at 30-32 weeks (the main group) were selected from the specified cohort. Two research groups were formed: group 1 – 40 patients with verified moderate oligohydramnios and group 2 – 40 patients with polyhydramnios. The control group included 30 somatically healthy pregnant women with a normal volume of amniotic fluid and a physiological course of pregnancy.

Inclusion criteria were: pregnancy with pathology of the fetal environment (change in amniotic fluid index value (hypohydramnios, polyhydramnios)), risk factors for the development of miscarriage, preeclampsia, fetal growth restriction, consent to participate in the study.

Exclusion criteria were: antiphospholipid syndrome, habitual miscarriage, acute respiratory diseases and inflammatory diseases during pregnancy, fetal malformations, refusal to participate in the study.

Verification of the diagnosis of oligohydramnios or polyhydramnios was based on the value of the amniotic fluid index (AFI), first revealed in 30–32 weeks of gestation during the period of the maximum volume of amniotic fluid [3, 6]. With an AFI from 5 cm to 10 cm (the lower norm), the diagnosis of moderate idiopathic oligohydramnios was verified; and with an AFI from 20 cm to 24 cm (the upper limit of the norm) – polyhydramnios was verified. AFI from 10 cm to 20 cm was accepted as the norm [3, 6].

Infectious status was assessed at 16 weeks of pregnancy by enzyme-linked immunosorbent assay (ELISA) and DNA polymerase chain reaction. Ultrasound examination was performed on the diagnostic device "Toshiba SAL – 38 AS". The study of the structural and functional features of the placenta and umbilical cord included sonographic, organometric, and macromorphoscopic methods.

The organometric method included measurement of placenta mass and its dimensions (maximum and minimum diameter, maximum and minimum thickness), diameter and thickness of the umbilical cord, as well as placental-fetal coefficient [2, 3, 6, 8]. During the macroscopic examination, the integrity of the placenta tissues and its reconstruction were determined. The shape of the maternal and fetal surfaces, as well as the umbilical cord, were studied.

When examining the maternal surface, the integrity of the decidual tissue, the shape and size of the placenta, the presence of accessory lobes, their number and size, expressiveness and depth of fissures were assessed. The expressiveness and depth of zones with atypical colour and density and the number of fresh and old blood clots were also noted.

When examining the fetal surface of the placenta, attention was paid to the shape and contours, the number of main vessels of the chorion, the colour of the amnion, the place of insertion of the umbilical cord, areas of damage, detachment, a rim on the placenta. The presence of deformations on the surface, namely, cysts and tumors, was noted. When examining the fetal membranes, their thickness, colour, inclusions (blood, meconium) and swelling were revealed. When evaluating the umbilical cord, special attention was paid to surface colour changes, length and thickness, helicity index, number of umbilical cord vessels, Wharton's jelly absence, etc.

For an objective assessment of the degree of reliability of the research results, a variational-statistical method of analysis of the obtained data was applied using a personal computer and an application program for working with Microsoft Excel spreadsheets using paired statistics methods "STATISTICA for Windows® – 6.0" package. Graphs were made with the help of Microsoft Excell 7.0 programs.

The research was conducted taking into account the main principles of the Helsinki Declaration on Biometric Research and the powers of the GCH ICH (1996), in accordance with biometric norms with compliance with the principles of confidentiality and ethics (excerpt from protocol No. 128/22 of the meeting of the Bioethics Commission dated 09/29/2022 Ivano-Frankivsk National Medical University, Ministry of Health of Ukraine).

RESULTS AND THEIR DISCUSSION

The average age of the patients included in the study was 30.4±3.2 years; first-time pregnant women and re-pregnant women accounted for almost the same proportions.

The main obstetric and perinatal risk factors were: spontaneous miscarriages in history (17.5%), infertility (27.5%), chronic endometritis (31.25%), preeclampsia in a previous pregnancy (22.5%). As demonstrated by

the results of pregnancies in both studied groups, a high proportion of repeated episodes of retrochorial hematomas (28.8%), early reproductive losses (16.3%), preeclampsia (41.3%), detachment of a normally placed placenta (7.5%), fetal death in utero (3.7%), fetal growth retardation syndrome (18.80%), fetal distress during pregnancy (28.8%) was diagnosed.

Taking into account the fact that one of the most frequent causes of the development of pathology of the fetal environment is a urogenital infection [1, 2, 14, 27], we evaluated the role of viral and bacterial agents in this category of patients. Determination of reproductively significant infections showed that the leading infection is ureaplasma, antibodies to which were detected in both studied groups, and the frequency of diagnosis is significantly higher (56.3% vs. 6.7% in the control group, p<0.001).

Viral associations were also significant as they were revealed in two thirds of the observations; 31 (77.5%) and 35 (87.5%) women of the studied groups were seropositive for the herpes simplex virus. Intergroup differences in the detection of both IgG and IgM were not established. In patients with pathology of the fetal environment, a comparison of markers of infectious factors and infection with different types of viruses revealed a more frequent carrier of cytomegalovirus; class G antibodies to cytomegalovirus were present in almost 90% of women, which significantly exceeded the indicators of the control group (p<0.05).

Some authors associate the manifestation of gestational complications with the reactivation of viruses of the herpes group [1, 2, 11, 14, 27]. Since infection with the above-mentioned viruses met with the same frequency, it is fair to say that the isolated effect of an infectious factor of a herpesvirus nature is of secondary importance, and its endothelial effect can be manifested in combination with the action of other pathological factors.

Thus, the active stage of reactivation of cytomegalovirus infection at the time of examination was diagnosed in our study with almost the same frequency of 10.0% in both groups, which is the evidence of the probability of an increase in the frequency of pregnancy complications as a result of the associative effect of herpesvirus infections; it also indicates a violation of immunoregulatory mechanisms as a result of the development of an anti-infective response and is a condition for the realization of gestational complications [1, 2, 11, 14, 27].

Sonographic monitoring of the structure of the placenta and umbilical cord in pregnant women of this category made it possible to present additional criteria for evaluating the functioning of the "mother-placenta-fetus" system, which contributes to a timely differentiated approach and the choice of rational obstetric tactics in this category of pregnant women.

Sonographic monitoring made it possible to note the following (Figure 1). As shown in Figure 1, in the case of pathology of the fetal environment in the first trimester of pregnancy, ultrasound signs of pathology of the embryo and extraembryonic structures were observed significantly more often than in the control group, namely, low placement of the fertilized egg was detected in 27 (33.8%) women, its deformation in 22 (27.5%) and partial separation of the chorion – in 23 (28.5%) women.

The progression of ultrasound criteria for dystrophic changes in the placental tissue was observed closer to 28–32 weeks (Figure 2). The following pathologies were diagnosed in pregnant women with pathology of the fetal environment: placental hypoplasia – in 24 (30.0%)
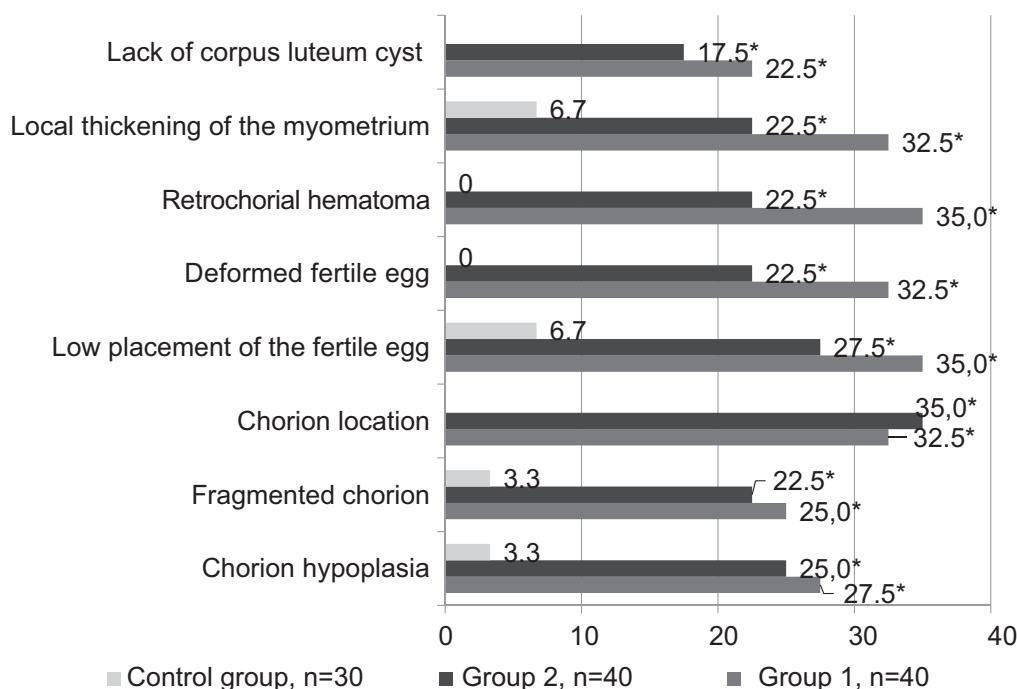

Figure 1. Echographic signs of the pathology of embryo and extraembryonic structures in the first trimester of pregnancy, %

Note. * – the difference is significant relative to the indicators of the control group, p<0.05.
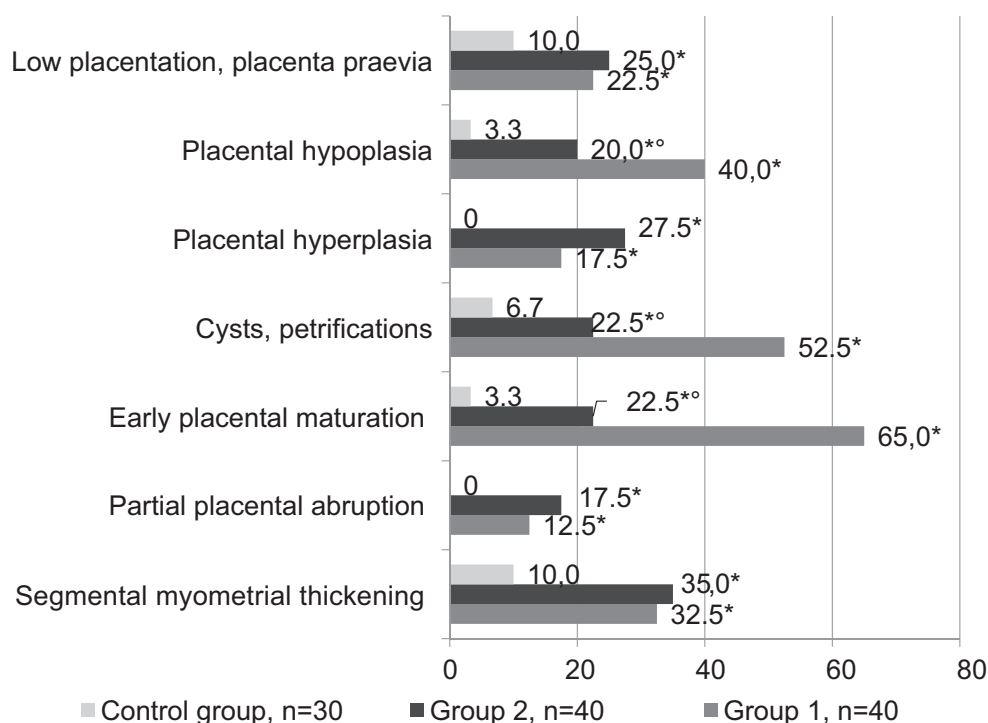
Figure 2. Placentography features in women with pathology of the fetal environment, %

Notes: 1. * – the difference is significant relative to the indicators of the control group, p<0.05; 2. ° – the difference is significant relative to the indicators of group 1, p<0.05.

women, signs of its early placental maturation – in 35 (43,8%) of pregnant women, and destructive changes (cysts, petrifications) – almost twice as often in the case of a small index of amniotic fluid (p<0.05). There were no significant differences in relation to other sonographic markers of placental pathology in the main studied groups.

Since the shape of placenta is an indirect reflection of the conditions of placentation, we conducted a postnatal study of the placenta and umbilical cord, which demonstrated the dominance of abnormal shapes in both main groups in the case of pathology of the fetal environment, in particular: a column-shaped shape in 36 (45.0%) versus 23 (76, 7 %) in the control, more often oval shape – 31 (38.8 %) versus 6 (20.0 %) in the control, or abnormal shape – 13 (16.3 %) versus 1 observation in the control (3.3 %), as well as the predominance of eccentric and marginal type of umbilical cord insertion (43 – 53.8 %), velamentous cord insertion (5 – 6.3 %), main and intermediate type of vascular branching (51 – 63.7 %) versus 4 cases in the control (13 .3%), which can be considered as evidence of the development of placental dysfunction in the early stages of gestation.

The so-called "thin" umbilical cord, where Wharton's jelly absence (<0.5 g/cm) was diagnosed in 9 cases (11.3%), "thick" umbilical cord (1.1 g/cm) – in 14 cases (17.5%), umbilical cord wrapping around the neck and other parts of the body – in 21 patients (26.3%), true umbilical cord knots – in 7 (8.8%), single umbilical artery syndrome was a rare case (1 – 1.3%). The length of the umbilical cord significantly exceeded the population norm in 31.3% of observations; an absolutely short um-

bilical cord was found in 9 people (11.3%), a combination of different characteristics of the umbilical cord was noted in a third of the observations (31.3%).

The weight of the placentas varied between 370–675 g, a decrease in the placental-fetal coefficient was noted in the main groups, first of all in the case of oligohydramnios (up to 0.11±0.01 U.U. vs. control data 0.16±0.01 U.U.). In 41.3% of placentas, single ischemic heart attacks located on the periphery were found.

A retrospective assessment of the concentration of the placental growth factor PlGF in the main group of patients, which belongs to the VEGF subfamily and has pronounced angiogenic properties, ensuring the proliferation of extravillous trophoblast [9, 21, 24, 26], made it possible to note in the period of 12–16 weeks of pregnancy in the case of fetal environment pathology a decrease in its average composite indicators by 2.3 times compared to control data; the most significant deviations in PlGF concentration were in patients with oligohydramnios (2.5 times compared to control data, p<0.05), which may be a marker of impaired formation of the fetoplacental complex with deterioration intrauterine condition of the fetus (the development of fetal growth retardation syndrome and fetal distress) (Figure 3).

It should also be noted a decrease in the level of free VEGF-1 compared to the control data at the stage of placentation – by 1.6 times in the indicated terms, as well as in the greater half of the samples 66.3% (53 observations) – already at the stage of preconception preparation.

The obtained results demonstrate the relationship between the disruption of the mechanisms of angiogenesis and the hemodynamics of the pelvic organs with
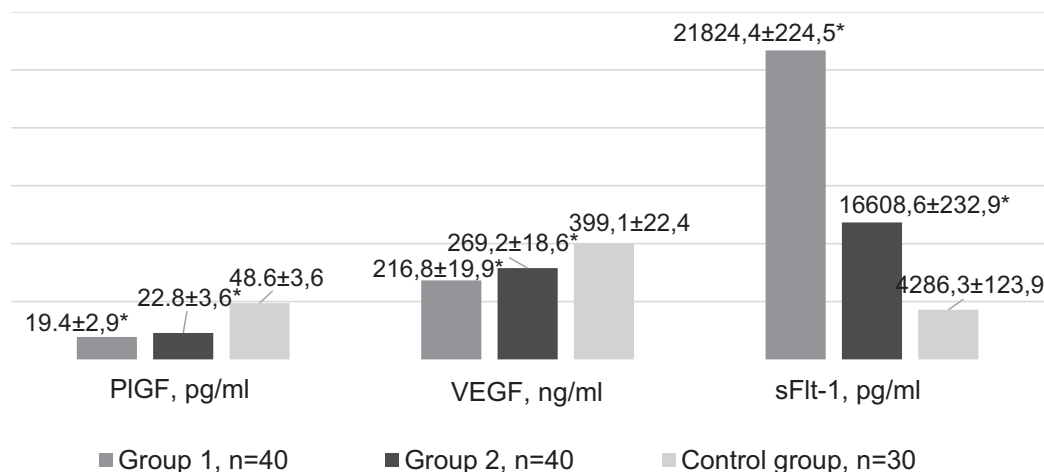
Figure 3. Concentration of growth factors in blood serum of patients of the studied groups at the stage of placentation, M±m
Note: * – the difference is significant relative to the indicators of the control group, p<0.05.

changes in the implantation capacity in patients with pathology of the fetal environment, which was naturally accompanied by a decrease in the angiogenic factor VEGF-1 in this category of pregnant women compared to control data (p<0.05).

At the same time, vascular imbalance is the leading factor in the development of placental dysfunction and its consequences. When analyzing the content of antiangiogenic growth factors in the blood serum, significant differences were obtained in the main groups of aggregated sFlt-1 indicators, which in the early stages of gestation indicated significantly higher parameters by 5.1 times compared to the average level of the control group (4286.3±123.9) pg/ml (p<0.05), which obviously led to the initiation of placental dysfunction and further deterioration of the intrauterine condition of the fetus. A more pronounced vascular imbalance already at the stage of preconception preparation led to its strengthening towards an increase in the level of antiangiogenic growth factors (sFlt-1) and the progression of placental dysfunction.

The assessment of the degree of angiogenesis imbalance made it possible to develop an algorithm for monitoring patients at risk of developing placental dysfunction, which required the formation of several groups with a likely unfavorable prognosis: women whose condition allows prolonging pregnancy and giving birth to a healthy fetus; patients whose condition allows prolonging the pregnancy, however, the development of placental dysfunction should be expected, which means that the monitoring of such a pregnancy should be more detailed, including the implementation of preventive measures, assessment of the infectious status and the use of antioxidant therapy and small doses of aspirin [7, 9, 13, 15, 21, 26], assessment of sonographic parameters of the state of the fetal environment, increasing the frequency of ultrasound examination and instrumental assessment of the intrauterine state of the fetus; as well as pregnant women with increased probability of reproductive losses and negative perinatal consequences, which requires optimizing the timing of childbirth.

In recent years, strong evidence of the hypothesis regarding the connection of adverse pregnancy outcomes with the state of the microbiota of the urogenital tract as a whole, and the secondary role of genital mycoplasmas has appeared [1, 2, 11, 14, 27]. It has been established that the persistence of infectious agents in the endometrium even at the stage of preconception preparation may not have a direct effect on the fertilized egg, but may be realized indirectly through the immune system or the hemostasis system, since under the influence of the infectious factor, the level of certain pro-inflammatory cytokines, which are the main initiators of pregnancy termination, increases in the first trimester [1, 2, 11, 14, 27].

Despite the fact that the development of obstetric and perinatal pathology largely depends on the presence of an active infectious process in the mother, currently most studies form a scientific position that the very fact of carrying viruses during pregnancy is not a necessary condition for the manifestation of pathogenetic properties of infectious agents. Obviously, a more significant condition for the realization of gestational complications is a violation of immunoregulatory mechanisms as a result of the development of an anti-infective response [1, 2, 11, 14, 27].

Thus, analyzing the infectious profile, it was established that in both groups, the frequency of suffering from urogenital infections and representatives of the TORCH group was practically identical, therefore, the infectious profile should be considered as a possible trigger for the initiation of endothelial damage and the development of placental dysfunction.

Currently, a scientific argument concerning the effect of hemostasis pathology on embryonic losses is worthy of attention, which intensifies the study of the influence of angiogenic processes and antiangiogenic factors on the consequences of implantation [9, 10, 12, 13, 15, 22]. A clear relationship between the normal function of the endometrium and the state of angiogenesis is traced in the scientific literature reviews.

The most important regulatory transmitters in growth factors are transforming factors, endothelial growth factors, among which special attention should be paid to the vascular endothelial growth factor (VEGF), an increase in the concentration of which was found in the blood serum during unsuccessful implantations of the fertilized egg. It is also known as vascular permeability factor or vasculotropin, and which is the most studied activator of angiogenesis [9, 16, 22, 24, 25]. According to the authors, the assessment of angiogenic and proangiogenic growth factors makes it possible to judge deep damage to the fertile egg and its vascular membrane and be used to control the effectiveness of preventive programs and the effectiveness of preconception preparation [17, 18, 20, 21, 23, 26].

The authors established that during pregnancy loss there is a decrease in the level of PlGF and the soluble VEGF receptor against the background of an increase in its level in blood serum [10, 12, 13, 16, 22], which allows us to consider VEGF as one of the key markers of vascular dysfunction in habitual miscarriage and the main indicator of endometrial insufficiency [9, 10, 20, 24, 25]. Thus, the analysis of modern scientific literature indicates a violation of the expression of proangiogenic factors in complicated pregnancy, although the pathogenesis remains not fully clarified [7, 9, 22, 24, 25].

The detected changes in the content of growth factors and vasoactive substances in the blood serum of such women are evidence that the development of the placenta is accompanied by a violation of the formation of its vascular system and a decrease in hemodynamics. In connection with the above, it is of interest to study the nature of production of the specified components in pathology of the fetal environment, which causes placental dysfunction and its impaired metabolic potential during implantation and placentation.

The results obtained above allow us to confirm the existing opinion that long before the clinical diagnosis of the specified condition in patients with pathology of the fetal environment, an imbalance of vascular growth factors is expressed, which is reflected in reliable deviations already at the stage of preparation for pregnancy and the formation of the placenta, and creates prerequisites for the development of placental dysfunction and related negative perinatal consequences.

CONCLUSIONS

In patients with pathology of the fetal environment, a pronounced vascular imbalance was diagnosed at the stage of placentation with a decrease in the concentration of the placental growth factor PlGF by 2.3 times compared to control data, where the most significant deviations in PlGF concentration were found in patients with oligohydramnios (by 2.5 times compared to control data, $p<0.05$), as well as a 1.6-fold decrease in the level of VEGF-1 and an increase in the parameters of the antiangiogenic growth factor (sFlt-1), which became a prerequisite for the disruption of placentation mechanisms and the progression of placental dysfunction.

An indirect reflection of the conditions of placentation were the results of postnatal examination of the placenta and umbilical cord, which demonstrated the predominance of abnormalities, eccentric and marginal types of umbilical cord insertion, main and intermediate types of vascular branching, an increase in the share of umbilical cord pathology (Wharton's jelly absence, anomalies of umbilical cord vessels) and a decrease of the placental-fetal coefficient in both studied groups, first of all in the case of oligohydramnios (up to 0.11±0.01 U.U. vs. control data 0.16±0.01 cu).

The further search for criteria for early prediction of the development of placental dysfunction and the creation of a diagnostic algorithm system and monitoring of such patients are promising.

Conflict of interest. The authors did not declare any conflict of interest.

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