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Undifferentiated connective tissue dysplasia as a risk factor for placental dysfunction

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Abstract
To determine the correlation of local non-progressive abruption of placenta and the development of placental dysfunction with undifferentiated connective tissue dysplasia (UCTD), we have conducted the case-consequence research with 100 patients. The research included two stages. At the first stage, all the predictors of this complication were divided into 4 groups: somatic anamnesis, obstetric, gynecological and infectious anamnesis, course of the given pregnancy and results of tests for Phase-II detoxification gene polymorphism. At the second stage, all the significant predictors were included in a multifaceted logistic regressive analysis.
The most significant causes of local non-progressive abruption of placenta at placental dysfunction are the following: UCTD (OR-18.86; 6.58-54.02), its visceral markers such as scoliosis (OR-5.76; 2.08-15.97), heart diseases (mitral valve prolapse, hypertensive neurocirculatory dystonia, supplemental chord) (OR-8.61; 3.11-23.83), myopia (OR-6.25; 2.26-17.29), platypodia (OR-4.49; 1.61-12.55), renal diseases (OR-7.94; 2.87-21.98).
The sheer presence of UCTD in this category of patients increases by 18 times the risk of disorder of trophoblast invasion and development of placental dysfunction.

Keywords: local placental abruption, undifferentiated connective tissue dysplasia, placental dysfunction, gene polymorphism.

1. Introduction
As it is known, connective tissue dysplasia includes a group of genetically and clinically polymorphic conditions that are considered to play and important role in the development of many pathological conditions [1, 4]. In the majority of cases clinicians have to deal with the so called undifferentiated forms of connective tissue dysplasia (UCTD), with prevalence of up to 70-80 % in the population [5, 6]. In obstetrics and gynecology this problem attracts special attention at present in view of the evidence of its influence on the course of gestation and labor, the perinatal morbidity and death rate [3]. There are known scientific sources that point out negative influence of connective tissue dysplasia both on the development of endometrium in the cycles preceding pregnancy and on the processes of development and invasion of chorion in early gestational period, there are also indications of the very fact of pregnancy increasing the manifestations of UCTD symptoms in the dynamics of the gestational process. However, the issue of UCTD influencing the course of early gestational period remains controversial and contestable. The genesis of local non-progressive abruption of chorion and placenta in pregnancy is influenced by many factors. Among them are inflammatory diseases of female genital organs, in particular chronic endometritis and intraamniotic infection, multifetation, uterine malformations, certain somatic diseases of the mother, etc. [7, 9]. At the same time, in spite of the high prevalence of UCTD, its role in the genesis of local non-progressive abruption of placenta and the development of placental dysfunction in the given category of patients is not sufficiently researched, which makes this study relevant.
This study aims at determining the role of UCTD in the genesis of local non-progressive abruption of placenta and the development of placental dysfunction.

2. Research Materials and Methods
To assess the risk factors for local non-progressive abruption of placenta, we have conducted the case-consequence research with 100 patients. The basic group consisted of 50 patients with local non-progressive abruption of placenta and the development of placental dysfunction in relation to it. The reference group included 50 women with normal term labor selected at random. The groups are comparable in terms of age and social characteristics.

In all the pregnant women we have studied the potential risk factors for local non-progressive abruption of placenta. The research included two stages. At the first stage, all the predictors of this complication were divided into 4 groups: somatic anamnesis, obstetric, gynecological and infectious anamnesis, course of the given pregnancy and results of tests for Phase-II detoxification gene polymorphism.

The diagnosis of placental dysfunction was done by ultrasonic examination of the placenta condition, examination of uterine and placental blood circulation, of blood flow in funic vessels and major fetal vessels with the use of ultrasonic scanners as well as by assessing the levels of placental proteins.

At the second stage, all the significant predictors were included in a multifaceted logistic regressive analysis. On the whole, over 100 potential risk factors were analyzed. The statistic analysis procedures were carried out by means of STATISTICA 6 and SPSS-20 packages. When verifying zero hypotheses, the accepted critical value of the statistic significance level was 0.05. To analyze the correlation between a single qualitative sign standing for a dependent effective indicator and a big number of qualitative signs, we used the multifaceted logistic regressive analysis with a stepwise algorithm of inclusion of predictors [11].

To determine the phenotypic markers of UCTD we used the following method of diagnosing phenotypic signs: light degree – when two major or six minor signs, according to Milkovska-Dimitrova's and Arkashova's classification, are identified; medium degree – when three-four major and two minor signs are identified, severe degree – with five and more major signs and three-four minor ones [8, 10]. The diagnosing was done by clinical/phenotypic examination of patients (taking into consideration their family anamnesis) and by instrumental examination methods (echocardiography and ultrasonic examination of the abdominal cavity organs and kidneys).

Since the basis for the development of UCTD lies in the metabolic disorder of collagen formation, we have analyzed the result of tests for carrying Phase-II detoxication gene polymorphism [2].

3. Research Results and Their Discussion

The UCTD prevalence in the reference group was 6 % and in all the women of this group it was of light degree, with no major signs and no more than six minor signs. In the basic group the UCTD prevalence was statistically significant – 72%, of which 50% had UCTD of light degree, 36.1% - of medium degree and 13.9% - of severe degree. The most frequent signs were myopia (in 46% of the examined women), scoliosis (54%), platypodia (38%), heart diseases (mitral valve prolapse, hypertensive neurocirculatory dystonia, supplemental chord) (42%), urinary system diseases (52%).

As for phenotypes, the most frequent one was MASS phenotype diagnosed in 55.5% of cases, of which 45% presented dysplasia of light degree, 35% - of medium degree and 20% of severe degree. The second most frequent phenotype was the marfanoid one – 30.5%, with dysplasia of light degree in 54.5% of the examined women, of medium degree in 36.4% and of severe degree in 9.1%. The Ehlers–Danlos syndrome phenotype was diagnosed in 10% of women of the basic group, of which no one presented dysplasia of severe degree, 60% had dysplasia of light degree and 40% that of medium degree. When assessing the risk of local abruption of chorion in the early gestational period, we found out that the very presence of UCTD increased it by 18 times (OR-18.86; 6.58-54.02). The most significant signs of UCTD considerably increasing the risk of local non-progressive abruption of placenta were scoliosis (OR-5.76; 2.08-15.97), heart diseases (mitral valve prolapse, hypertensive neurocirculatory dystonia, supplemental chord) (OR-8.61; 3.11-23.83), myopia (OR-6.25; 2.26-17.29), platypodia (OR-4.49; 1.61-12.55), renal diseases (OR-7.94; 2.87-21.98).

In the set of factors representing obstetrical and gynecological anamnesis, the risk of local non-progressive abruption of placenta and, as a result, placental dysfunction, was credibly higher in cases of spontaneous abortion and intrauterine death (OR-3.45; 1.22-9.76) before the given gestational process, premature rupture of membranes (PROM) and premature labor in anamnesis (OR-8.29; 2.99-23.01).

The analysis of the course of the given pregnancy has shown that local non-progressive abruption of placenta was more often preceded by a clinically significant threat of abortion in the first gestational trimester (OR-10.13; 3.65-28.12).

In spite of lack of clear-cut differences, we found out that in the group of women with local non-progressive abruption of placenta, placental dysfunction diagnosed before the 20th week of gestation occurred 2.6 times more often: 22.2% vs. 8.3% (OR-3.17; 1.43-7.02). It is the early start of disorder of placental perfusion that accounts for arrested intrauterine development of the fetus in every fourth patient of the basic group, which is credibly higher than in the reference group ($p<0.05$). Recurrent cases of bloody discharge are also a credible predictor of placental dysfunction, increasing the risk of the latter by 5 times ($p<0.05$).

There is also a close link between placental dysfunction related to local non-progressive abruption of placenta and inflammatory diseases of the genital tract, in particular chronic endometritis, asymptomatic bacteriuria and bacterial vaginosis (OR-11.96; 4.29-33.40). In our research, we should note a significant percentage of genital infections in the examined patients. For instance, bacterial vaginosis was diagnosed in 62% of cases, nonspecific bacterial vaginitis – in 48% of the examined patients. Obviously, bacterial infections increase the risk of local non-progressive abruption of placenta by 11 times.

At present there are not many studies searching for the genetic markers of placental dysfunction and the data on their association with the development of the said pathology are controversial. When analyzing scientific sources, we came across only isolated pieces of information dealing with the study of glutathione-S-transferase gene polymorphism at placental dysfunction in relation to habitual prematurity [7]. Yet, the number of works dealing with the research of the intensity of free radical processes and the antioxidant state of women with placental dysfunctions and prematurity is growing from year to year [12, 13]. As it is known, the role of placenta is determined by the realization of a number of functional mechanisms – trophism and protein synthesis, hormonal function and hormonal modulation, synthesis of biologically active substances, antitoxic function of metabolite discharge, regulation of the processes of lipid peroxidation and antioxidant protection. Glutathione-S-transferase takes active part in the neutralization of lipid peroxidation products and peroxides of DNA, reducing organic hydroperoxides to alcohols and isomerizing some steroids and prostaglandins. The intensification of lipid peroxidation is known to be linked with the detoxification system polymorphism and it produces a toxic effect on cell membranes. It is also proved that imbalance in the system of lipid peroxidation - antioxidant protection may also be caused by a decrease in the

concentration of steroid hormones that possess antioxidant properties, which also influences the pathogenesis of placental dysfunction. Thus, one may assume that certain glutathione-S-transferase gene polymorphisms lead to the exhaustion of the glutathione-dependent antioxidant protection and inhibition of the detoxification function of placenta, which results in the progression of placental dysfunction. These data confirm indirectly the involvement of detoxification systems in the development of this pathology.

The conducted research has found in women with local non-progressive abruption of placenta and placental dysfunction related to it a credible increase in the frequency of the GSTM1 0\0 genotype "functionally weakened" by one gene and the combination of "functionally undesirable" genotypes by two (GSTM1 0\0+ GSTT1 0\0) and three genes (GSTM1 0\0+ GSTT1 0\0+ GSTP1 A\S and GSTM 0\0+ GSTT 0\0+ GSTP1 S\S) ($p<0.05$). And women with the GSTM1 0\0 genotype present a higher risk of disorder of trophoblast invasion, which manifests itself clinically in local non-progressive abruption of placenta (OR-4.49; 1.61-12.55).

The inclusion of all the most significant factors studied in this research in the regressive model has enabled the identification of the most independent and constant among them, while the significance of other potential risk factors decreased after the adjustment.

The data obtained by us show that local non-progressive abruption of placenta is the result of many factors that produce their effect in various, often intersecting pathophysiological ways and it's hardly possible to single out the predominant etiological factor.

4. Conclusions

The prevalence of undifferentiated connective tissue dysplasia is credibly higher in the group of women with local non-progressive abruption of placenta and placental dysfunction related to it than in healthy pregnant women.

The predominant phenotype is MASS phenotype while the Ehlers-Danlos syndrome phenotype is less frequent.

A credibly high percentage of UCTD in women with local non-progressive abruption of chorion and placenta is a risk factor for the development of disorders of the reproductive function. The sheer presence of UCTD in this category of patients increases by 18 times the risk of disorder of trophoblast invasion and development of placental dysfunction. The most significant visceral markers here are scoliosis, myopatia, platypodia, cardiopathy and diseases of the urinary system. Women with the GSTM1 0\0 genotype present higher risk of disorder of trophoblast invasion, which manifests itself clinically in local non-progressive abruption of placenta (OR-4.49; 1.61-12.55).

The significant prevalence of undifferentiated connective tissue dysplasia (from 30 to 80 %) and low controllability of this risk factor account for the necessity of defining the criteria of regular medical check-up of pregnant women and of further research and accumulation of knowledge in terms of clinical significance of this nosology in the course of the gestational process.

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