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## The effect of preventive therapy for placental dysfunction on uteroplacental blood flow in pregnant women with low-lying placenta

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The mother's health and the quality of placental formation in early pregnancy determine the course of gestation, fetal development, and neonatal prognosis. One of the key disorders that negatively affects these processes is placental dysfunction, in the development of which low chorionic attachment plays a special role, disrupting implantation and vascularization of the placenta.

**Aim** – to evaluate the effectiveness of a complex of preventive measures for the formation of uteroplacental blood flow in pregnant women with low chorionic localization in early pregnancy.

**Materials and methods.** A total of 119 pregnant women were observed: 64 patients received preventive therapy (micronized progesterone, ginkgo biloba, folic acid, and magnesium) from early gestation and 55 patients were in the control group without preventive intervention. Doppler parameters of the right and left uterine arteries and spiral arteries were evaluated, as well as the morphofunctional characteristics of the chorion using three-dimensional VOCAL technology (chorion volume, vascularization index).

**Results.** In patients of the main group, there was a significant decrease in resistance indices in the uterine and spiral arteries, an increase in diastolic and mean blood flow velocities by 30-40%, an increase in chorionic volume ( $62.0 \pm 4.1 \text{ cm}^3$  vs.  $48.1 \pm 3.8 \text{ cm}^3$ ) and its vascularization (vascularization index –  $17.8 \pm 0.38$  vs.  $9.68 \pm 0.12$ ) compared to the control group. The data indicate an improvement in the hemodynamics of the «mother–placenta–fetus» system and more effective formation of the fetoplacental complex.

**Conclusions.** Early application of the proposed complex of preventive measures in pregnant women with low-lying placenta contributes to the normalization of uteroplacental blood flow, improves chorionic vascularization, and reduces the risk of developing primary placental dysfunction, which provides favorable conditions for fetal development.

The study was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

The author declares no conflict of interest.

**Keywords:** placental dysfunction, low placentation, preventive therapy, uteroplacental blood flow, Dopplerometry.

### Вплив профілактичної терапії плацентарної дисфункції на матково-плацентарний кровотік у вагітних із низькою плацентажією

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Стан здоров'я матері та якість формування плацентарного комплексу на ранніх термінах вагітності визначають перебіг гестації, розвиток плода та неонатальний прогноз. Одним із ключових порушень, що негативно впливає на ці процеси, є плацентарна дисфункція, особливою роллю у розвитку якої відіграє низьке прикріплення хоріону, що порушує імплантацію та васкуляризацію плаценти.

**Мета** – оцінити ефективність комплексу профілактичних заходів щодо формування матково-плацентарного кровотоку у вагітних із низькою локалізацією хоріону на ранніх термінах гестації.

**Матеріали та методи.** Під спостереженням перебували 119 вагітних: 64 пацієнтки отримували профілактичну терапію (мікронізований прогестерон, гінкго білоба, фолієва кислота та магній) із ранніх термінів гестації, 55 – контрольна група без профілактичного втручання. Оцінено доплерометричні показники правої та лівої маткових артерій і спіральних артерій, а також морфофункціональні характеристики хоріону за допомогою тривимірної технології VOCAL (об'єм хоріону, індекс васкуляризації).

**Результати.** У пацієнток основної групи спостерігалось достовірне зниження резистентних індексів у маткових та спіральних артеріях, підвищення діастолічних і середніх швидкостей кровотоку на 30-40%, збільшення об'єму хоріону ( $62,0 \pm 4,1 \text{ см}^3$  проти  $48,1 \pm 3,8 \text{ см}^3$ ) та його васкуляризації (індекс васкуляризації –  $17,8 \pm 0,38$  проти  $9,68 \pm 0,12$ ) порівняно з контрольною групою. Дані свідчать про покращення гемодинаміки системи «мати–плацента–плід» та більш ефективне формування фетоплацентарного комплексу.

**Висновки.** Раннє застосування запропонованого комплексу профілактичних заходів у вагітних із низькою плацентажією сприяє нормалізації матково-плацентарного кровотоку, покращує васкуляризацію хоріону та знижує ризик розвитку первинної плацентарної дисфункції, що забезпечує сприятливі умови для розвитку плода.

Дослідження виконано відповідно до принципів Гельсінської декларації. На публікацію отримано інформовану згоду пацієнток.

Автор заявляє про відсутність конфлікту інтересів.

**Ключові слова:** плацентарна дисфункція, низька плацентажія, профілактична терапія, матково-плацентарний кровотік, доплерометрія.

## Introduction

The mother's health during pregnancy and the quality of placental complex formation are crucial for the course of gestation, fetal development, and neonatal prognosis. One of the important disorders that negatively affects these processes is placental dysfunction (PD) – a pathological condition in which the functional activity of the placenta decreases, leading to fetal distress, fetal growth retardation, and other serious complications [1].

One of the key risk factors for PD is low chorionic implantation in early pregnancy (up to 12 weeks). This condition can occur as a result of endometrial defects, inflammatory processes, hormonal disorders, or the consequences of previous surgical interventions. As a result, normal implantation and vascularization of the chorion are disrupted, leading to the formation of an incomplete placental bed and pathological changes in the spiral arteries, which are critical for adequate uteroplacental blood flow [2,3].

The pathogenetic basis of PD lies in the processes of cytotrophoblast invasion into the spiral arteries. Insufficiency of the first wave of trophoblast invasion prevents the formation of adequate uteroplacental blood flow, while disruption of the second wave of invasion leads to ineffective increase in placental blood supply, imbalance of the lipid peroxidation system, increased permeability of the placental barrier, and damage to cell membranes. Today, it is generally accepted that both pregnancy loss and the development of gestational complications are directly related to disturbances in both waves of trophoblast invasion [2,4,7].

Thus, early detection of placental lesions is critical for ensuring normal fetal development and predicting the course of pregnancy. That is why the current task of modern perinatology is to form risk groups for the development of PD already in the first trimester of gestation.

Despite the availability of modern diagnostic methods, including ultrasound and Doppler studies, the question of effective prevention of PD in low placental attachment remains open. It is known that early detection of signs of impaired blood flow and timely administration of pathogenetically justified drug therapy can significantly improve uteroplacental hemodynamics, promote better chorionic vascularization, normalize placental hormonal function and, as a result, reduce the frequency of gestational complications [6,8,9].

In view of the above, it is important to study the effect of the complex of preventive measures we pro-

pose on uteroplacental blood flow indicators, morpho-functional characteristics of the placenta, as well as on the overall course of pregnancy in women with low chorionic location in the first trimester of gestation.

*The aim* of the study is to evaluate the effectiveness of a set of preventive measures for the formation of uteroplacental blood flow in pregnant women with low chorionic localization in early gestation based on the analysis of Doppler characteristics and three-dimensional (3D) imaging indicators.

## Materials and methods of the study

We observed 119 pregnant women with low chorionic location. The main group consisted of 64 patients who underwent prevention of PD from early gestation using a complex of drug therapy developed by us. The control group consisted of 55 women with similar pathology who did not undergo any preventive intervention for PD in the first trimester of pregnancy.

The groups of pregnant women examined were representative in terms of age and social status. Women with multiple pregnancies, pregnancies after assisted reproductive technologies, as well as patients with severe somatic diseases, congenital or acquired uterine abnormalities, and cases of detected fetal malformations were excluded from the study. This approach made it possible to reduce the influence of potential factors that could distort the results of the assessment of uteroplacental blood flow formation.

In order to optimize trophoblast invasion and stimulate the establishment of effective uteroplacental blood flow in the first trimester of gestation with low chorionic localization in women of the main group, a complex of preventive therapy was used. The main component of treatment was micronized progesterone at a dose of 100 mg twice daily vaginally. The drug, identical in structure to endogenous progesterone, does not have a pronounced antigonadotropic effect at the prescribed doses, but promotes secretory transformation of the endometrium and provides the necessary conditions for the formation of fetal-chorionic blood flow. Progesterone therapy was prescribed from the moment of diagnosis of low chorionic attachment (6–7 weeks of gestation) and continued until the end of the placentation period (16–17 weeks), provided that there was a positive trend in Doppler blood flow parameters. The preventive complex also included: ginkgo biloba extract (40 mg three times a day), which improves

Table

**Indicators of Doppler examination of blood flow in the uterine and spiral arteries at 9–12 weeks of pregnancy**

Parameters	Indicators	Main group (n=64)	Control group (n=55)
Right uterine artery	S/D ratio	5.9±0.5*	7.4±0.6
	RI	0.67±0.04	0.75±0.06
	PI	1.1±0.14*	1.7±0.16
	PSV, cm/s	60.2±2.9	56.3±2.7
	EDV, cm/s	17.8±1.1*	13.6±0.9
	MDV, cm/s	16.8±1.2	14.6±0.9
Left uterine artery	S/D ratio	5.8±0.5*	7.5±0.6
	RI	0.70±0.05	0.81±0.07
	PI	1.2±0.14*	1.7±0.18
	PSV, cm/s	64.1±2.7	59.8±2.3
	EDV, cm/s	18.8±1.1*	13.5±0.9
	MDV, cm/s	13.2±1.0	10.9±0.8
Spiral arteries	S/D ratio	2.0±0.4*	3.4±0.5
	RI	0.4±0.07*	0.7±0.08
	PI	0.8±0.08*	1.2±0.10
	PSV, cm/s	59.4±2.5	55.1±1.6
	EDV, cm/s	28.7±1.4*	20.4±1.3
	MDV, cm/s	28.4±1.8*	19.8±1.7

Note:\* – the difference is significant compared to the control group ( $p < 0.05$ ).

microcirculation and contributes to improved blood supply to the trophoblast due to its vasodilating effect; Folio 1 tablet per day in the morning with food), containing 400 mcg of folic acid and 200 mcg of potassium iodide, used to prevent congenital malformations of the fetus; Bioelectra 1 tablet per day), which provides 300 mg of magnesium ions to maintain uterine tone and stabilize placental perfusion. The course of non-hormonal therapy lasted an average of 12–14 days, was prescribed from 5–8 weeks of gestation, and was repeated 2–3 times during the first half of pregnancy at intervals of 2–3 weeks. Women in the control group received only folic acid. Thus, the therapy used in the main group was aimed at improving perfusion in the area of chorionic attachment and ensuring proper formation of uteroplacental blood flow in the early stages of gestation.

All participants in the study underwent a comprehensive ultrasound examination. At 9–12 weeks of gestation, within the first trimester, a transvaginal ultrasound examination was performed using 3D VOCAL (Virtual Organ Computer-aided AnaLysis) technology, which was used to determine the volume of the chorion and analyze its vascular architecture.

The vascularization of the chorion was assessed by automated calculation of the vascularization index (VI), which reflects the functional density of vascular elements in the entire volume of the placenta, allowing for objective characterization of its blood supply. In addition, all patients underwent Doppler assessment of uteroplacental blood flow. An analysis was performed of resistance indices (RI): pulsatility index (PI), systolic-diastolic ratio (SDR) and blood flow velocity characteristics in the right and left uterine arteries (UA) and spiral arteries (SA), peak systolic velocity (PSV), end-diastolic velocity (EDV), mean diastolic velocity (MDV), which allowed for a comprehensive assessment of the functional state of early placental blood flow [5,7,8].

Statistical analysis was performed using standard methods of variational statistics. Student's t-test was used to assess the significance of differences between indicators. Results were considered statistically significant at  $p \leq 0.05$ .

### Results of the study and discussion

Clinical observation allowed us to evaluate the effectiveness of the proposed set of preventive mea-

tures in pregnant women with low placentation, starting from early gestation. The state of uteroplacental blood flow, Doppler parameters, and morpho-functional characteristics of the placental bed in the main and control groups were analyzed. The results obtained allow us to draw conclusions about the advantages of early prevention of PD in cases of low chorionic location. The results of the study are presented in Table.

Compared with the control group, pregnant women in the main group showed a significant decrease in resistance indices in the right uterine artery: the ratio of systolic to diastolic velocities (S/D ratio) was  $5.9 \pm 0.5$  versus  $7.4 \pm 0.6$ , which is 20.3% lower, and the PI was  $1.1 \pm 0.14$  versus  $1.7 \pm 0.16$ , i.e., a decrease of 35.3% ( $p < 0.05$ ). A similar trend was observed in the left uterine artery, where the S/V ratio was  $5.8 \pm 0.5$  versus  $7.5 \pm 0.6$  (a decrease of 22.7%), and the RI was  $1.2 \pm 0.14$  versus  $1.7 \pm 0.18$  (a decrease of 29.4%;  $p < 0.05$ ). The RI was also lower in pregnant women in the main group, although the difference was not statistically significant ( $p > 0.05$ ). Thus, compared with the control group, the main group showed a significant decrease in resistance indices in the right and left uterine arteries, indicating improved hemodynamics in the uteroplacental bed. The decrease in S/D ratio and PI, as markers of vascular resistance, indicates a reduction in placental hypoperfusion and a potentially lower risk of PD. Although the decrease in IR was not statistically significant, the overall trend toward improved blood flow confirms the effectiveness of the prevention measures taken [8].

At the same time, there was a significant increase in blood flow velocity parameters: the EDV in the right uterine artery was  $17.8 \pm 1.1$  cm/s compared to  $13.6 \pm 0.9$  cm/s in the control group (an increase of 30.9%), and in the left uterine artery –  $18.8 \pm 1.1$  cm/s compared to  $13.5 \pm 0.9$  cm/s (an increase of 39.3%). The results obtained indicate an improvement in placental perfusion and an increase in its functional capacity in the early stages of gestation.

The study of blood flow in the spiral arteries also showed significant advantages in patients in the main group. They showed a decrease in RIs (SDS –  $2.0 \pm 0.4$ ; IR –  $0.4 \pm 0.07$ ; PI –  $0.8 \pm 0.08$ ), in contrast to the control group (SDS –  $3.4 \pm 0.5$ ; IR –  $0.7 \pm 0.08$ ; PI –  $1.2 \pm 0.10$ ), confirming the effectiveness of preventive measures ( $p < 0.05$ ). This indicates a more complete transformation of the spiral arteries, which is critical for adequate placental blood supply.

Also, in the group receiving PD prevention, diastolic and mean blood flow velocity in the spiral arteries were significantly higher, by almost 30–40% compared to the control group ( $p < 0.05$ ). The resistance of the spiral arteries in women receiving preventive treatment was significantly reduced by almost one-third compared to the control group. These data indicate the effectiveness of early preventive therapy in normalizing the hemodynamics of the spiral arteries and a potentially beneficial effect on fetal development.

In addition, the morphofunctional state of the chorion was assessed. At 9–12 weeks of gestation, its volume was significantly larger in patients who received prophylactic treatment ( $62.0 \pm 4.1$  cm<sup>3</sup> vs.  $48.1 \pm 3.8$  cm<sup>3</sup>), which reflects more intensive formation of the future placenta and contributes to its adequate functioning. The increase in chorionic volume can be regarded as a consequence of better trophoblastic invasion and more active development of the villous tree, which ensures effective exchange between the maternal and fetal-placental blood flow [9].

The VI was also significantly higher in the main group ( $17.8 \pm 0.38$ ) compared to the control group ( $9.68 \pm 0.12$ ), indicating enhanced angiogenesis and the formation of a denser network of vessels in the chorionic implantation zone. This, in turn, creates favorable conditions for a more efficient blood supply to the placenta. A similar trend was observed in the analysis of the blood flow index:  $45.6 \pm 3.1$  in patients in the main group versus  $35.1 \pm 2.8$  in the control group, indicating more active chorionic perfusion, i.e., increased exchange of oxygen and nutrients in the early stages of fetoplacental complex formation. These changes are consistent with the data obtained on the reduction of vascular resistance in the uterine arteries and the increase in blood flow velocity indicators, which together confirm the positive effect of the prevention measures taken on the establishment of placental blood circulation.

## Conclusions

The results of the study indicate that the use of the developed complex of therapeutic and preventive measures from early gestation in pregnant women with low chorionic location has a positive effect on the formation and establishment of uteroplacental blood flow. The observed significant decrease in resistance indices in the uterine arteries, increase in blood flow velocity parameters, increase in chorionic

volume and its vascularization indicators indicate an improvement in hemodynamics in the «mother–placenta–fetus» system. This, in turn, provides optimal conditions for trophoblast development, adequate placental perfusion, and effective transplacental exchange of oxygen and nutrients.

Thus, conducting a complex of preventive therapy from early pregnancy in women with low-lying placenta contributes to the formation of a full-fledged fetoplacental complex, improves blood supply to the placenta, and reduces the risk of developing primary

PD. The use of this complex is recommended for the prevention of PD and the reduction of the frequency of adverse perinatal outcomes in high-risk groups.

**Prospects for further research.** In the future, it is planned to predict the development of perinatal pathology in pregnant women with morphological and functional disorders of the chorion-placental complex in early gestation in the presence of low chorion localization.

*The author declares that there is no conflict of interest.*

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