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COMBINED PREVENTION OF FETAL GROWTH RESTRICTION BASED ON DETERMINATION OF DIAGNOSTIC MARKERS

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Abstract

Due to the morbidity of mothers and newborns caused by fetal growth restriction (FGR) and preeclampsia, preventive measures should be taken, especially in women at high risk of developing these conditions. Many studies have been conducted on the prevention of FGR and preeclampsia in high-risk women, especially anticoagulants, aspirin, paravastatin, nitric oxide, microelements (L-arginine, folic acid, vitamins E and C, phytonutrients, vitamin D) and calcium.

The aim is to improve perinatal consequences by preventing FGR in high-risk women.

Materials and methods: A prospective study of 137 pregnant women in the period of 11^0–13^6 weeks was conducted at the Perinatal Center in Kyiv. Pregnant women were divided into 3 groups. The main group included 47 women at high risk of FGR who received therapy (low doses of aspirin, low molecular weight heparin (LMWH) and vitamin and micro elements drugs). The comparison group included 45 women who had a high risk of FGR but did not receive treatment. The control group consisted of 45 women who were not at risk of FGR. The frequency of FGR and placental dysfunction were analyzed as well as a fetal distress was analyzed ante- and intranatally.

Results: Therapy with low doses of aspirin, LMWH and a complex preparation of vitamins and micro elements improves the course of pregnancy and gestational complications. In the main group FGR was detected in 8.5 %, in the comparison group – in 17.8 %, in the control group – 4.4 %. Placental dysfunction was detected in 13.3 % in the control group, and only 6.4 % in the main group that was close to the control group – 2.2 %. Similar tendencies were found for fetal distress ante- and intranatally.

Conclusions: The proposed prophylactic measures can improve maternal outcomes by reducing the level of gestational complications in pregnant women with biochemical signs of risk of FGR development. In addition, these preventive measures can reduce the frequency of children births with growth restriction, which significantly reduces early neonatal and perinatal morbidity and mortality.

Keywords: Aspirin, low molecular weight heparin (LMWH), fetal growth restriction, pregnancy-associated plasma protein A (PAPP-A), mean platelet volume (MPV), ultrasound diagnostics (USD).

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1. Introduction

Fetal growth restriction involves conditions under which the fetus does not reach its full growth potential. FGR is difficult to determine and measure, so small for gestational age (SGA) fetus, determined by centile weight, is often used as the most reliable marker. FGR and SGA can be caused by fetal problems such as chromosomal abnormalities, genetic syndromes and fetal infections; maternal disease; environmental toxins. The most common cause of FGR and SGA is placental insufficiency. The study focuses on options for FGR prevention, which are closely related to the development of placental insufficiency and preeclampsia.

Prescribing aspirin to prevent FGR, as shown by a recent meta-analysis of large-scale studies and a meta-analysis of individual patient data, significantly reduces fetal malnutrition (FM) in high-risk mothers (relative risk, 0.9–0.95 % confidence interval, 0.81–1.00). Aspirin in doses > 100 mg starting at 16 weeks of pregnancy or earlier should be recommended. These results are supported by the recommendations of national practical guidelines. Aspirin has a number of effects at the vascular level that can prevent the development of FGR (**Fig. 1**). For many years, it has been clear that aspirin inhibits the production of prostaglandins and thromboxane by irreversible inactivation of the enzyme cyclooxygenase. Thromboxane is a potent vasoconstrictor and prothrombotic antiplatelet agent. Prolonged intake of low doses of aspirin irreversibly blocks the formation of thromboxane A2 in platelets, inhibiting their aggregation. Recently, researchers have drawn attention to new cytoprotective and antioxidant mechanisms of aspirin that are independent of cyclooxygenase inhibition. Aspirin acetylates endothelial nitric oxide synthase, which leads to the release of nitric oxide from the vascular endothelium [1]. In addition, aspirin increases the activity of hemoxygenase-1 in endothelial cells to catabolize heme, which leads to a decrease in oxidative stress, damage and inflammation [2]. Most aspirin studies have focused on the treatment of preeclampsia as the primary outcome, with FGR therapy included only as a secondary outcome. However, the volume and quality of the obtained evidence allows to interpret and to implement these research results in a meaningful way. In 2018, systematic reviews based on a meta-analysis at the research level [3] and a meta-analysis of individual patient data [4] from randomized trials of aspirin and other antiplatelet agents were published simultaneously, including 20,909 and 32,217 women, respectively. Both analyzes confirmed the available evidence that aspirin provides a slight reduction in the risk of FGR and GP (less than 5 or less than the 10th percentile) at birth (analysis of individual patient data, relative risk, 0.9–0.95 % confidence interval [CI] 0, 81–1.00).

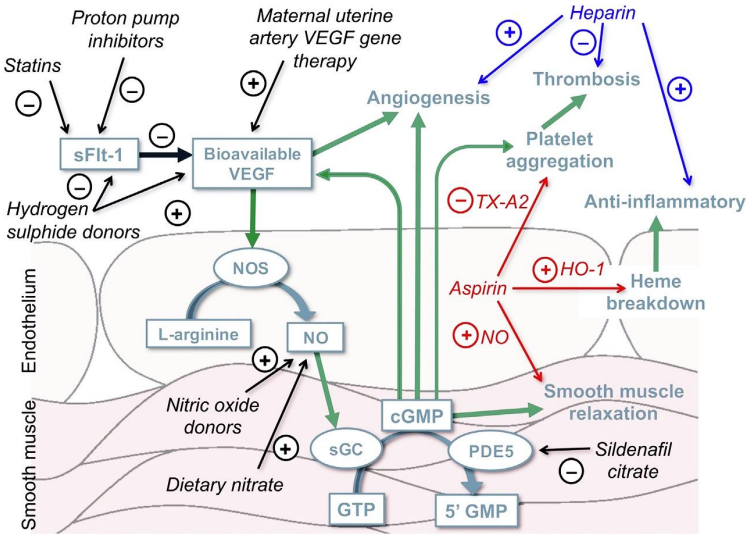

Fig. 1 Pathogenetic mechanisms of placental dysfunction

The results of *in vitro* and *in vivo* studies suggest that the administration of low molecular weight heparin may prevent FGR; however, the evidence from randomized controlled trials is conflicting. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) during pregnancy are commonly used for thromboprophylaxis and treatment of venous thromboembolism. Recently, LMWH has been preferred to UFH, which is a safe and effective drug for these indications [5]. Initial interest in the use of heparins for the prevention of placental pathologies was focused on their anticoagulant properties and the presumed ability to prevent thrombosis and subsequent placental infarction, which leads to miscarriage. *In vitro* and *in vivo* data suggest that heparins have various additional biological properties, including anti-inflammatory [6], complement inhibition [7], and antitumor [8], and are pro-angiogenic (**Fig. 1**). These additional effects can positively affect trophoblast development and invasion, making heparins potential candidates

for the prevention of placental-mediated pregnancy complications, including FGR. A meta-analysis of multicenter studies does not show any positive prophylactic effect of low molecular weight heparin on the primary rate of placental-mediated complications, including FGR (95 % confidence interval) [9]. Thus, low molecular weight heparin will be prescribed only in the conditions of this study, as one of the drugs for the combined prevention of FGR.

One of the pathogenetic links in the development of placental dysfunction is micronutrient deficiency, so the option to prevent gestational complications is to prescribe a complex drug containing 5 carefully selected components for a pregnant woman. This drug contains fish oil (doxahexaenoic acid) in a dose of 200 mg, folic acid (vitamin B9) – 400 μg, cholecalciferol (vitamin P3) – 5 μg, natural vitamin E (a-tocopherol) – 12 mg, potassium iodide – 150 μg.

Scientists are now looking forward to obtaining the results of randomized controlled clinical trials with sildenafil therapy [10] in predicting fetal growth restriction with early onset. Another approach is to focus on improving uteroplacental circulation with new therapeutic drugs. One of the most advanced methods is gene therapy using endothelial factor of uterine vascular growth, which is introduced into clinical practice by gene therapy specialists [11].

Other approaches using targeted therapy include the use of nanoparticles and miRNAs for local delivery of drugs to the endothelium of the uterine arteries or trophoblast [12].

The aim of this study was to evaluate the complex prophylactic therapy of pregnant women with existing risk factors for FGR in the first trimester, namely a decrease in PAPP-A, an increase in MPV and an increase in pulsation index and resistance index in uterine arteries.

2. Materials and methods

The prospective study was conducted on the basis of a specialized women's clinic of the Kyiv Perinatal Center during 2018–2020. The study included patients who were registered in a specialized women's clinic during gestation 11^0 – 13^6 weeks. The pregnancy was observed in a specialized women's clinic, and further delivery was performed at the Kyiv Perinatal Center. Pregnant women were divided into 3 groups. The formation of the groups was based on the ultrasound and laboratory signs of high risk of fetal growth restriction detected during the first combined screening – PAPP value less than 0.5 IU, increase in mean platelet volume over 10 fl, increase in pulsation index of uterine arteries over 1.34 and resistance index over 0.65. The main group included 47 pregnant women with two or more of the above criteria for high risk of fetal growth restriction, who from the moment of inclusion in the study were prescribed a set of preventive measures: aspirin at a dose of 75 μg per day, low molecular weight heparin at a prophylactic dose, specified by the manufacturer and complex drug of vitamins and microelements. The comparison group included 45 pregnant women in whom risk criteria for fetal growth restriction were identified in the first trimester, but they did not receive preventive treatment. The control group consisted of 45 women without risk factors for fetal growth restriction during the examination in the first trimester. The study did not include patients with multiple pregnancies and a high risk of genetic abnormalities.

The study at the planning stage passed the examination of the bioethics committee of the National University of Health named after P. L. Shupyk No. 8 from 23.10.2017. All pregnant women who participated in the study were offered informed consent, which contained a description of the study, the potential benefits and harms of participating in and refusing to participate in the study. After signing the consent, a copy was provided to the patient. The examination states that the design of the study complies with the Helsinki Declaration.

Groups of pregnant women were suitable for comparison by age and parity. The average age of pregnant women in the main group was 25.5 ± 3.3 years, in the comparison group – 26.5 ± 3.4 years, in the control group – 27.3 ± 3.1 ($p < 0.05$). In all groups, women giving birth for the first time predominated – 72.3 % in the main group, 66.7 % – in the control group, 71.1 % – in the comparison group ($p < 0.05$).

During the observation, patients underwent ultrasound monitoring at the scheduled time – at 20–21 weeks and at 32–34 weeks. In addition, at each visit to the women's clinic the height of the uterine fundus was measured. At a decrease in growth from 2 cm / week, ultrasound fetometry with

dopplerometry was repeated out of plan. In the dynamics of observation the frequency of diagnosis of fetal growth restriction (estimated mass less than the 10th percentile), uteroplacental circulation (slow blood flow in the umbilical artery), fetal distress before labor (zero or reverse blood flow in the umbilical artery, assessment of the umbilical artery, fetal profile 5 points or less) and fetal distress in childbirth (abnormal CTG assessment by NICE criteria) were analyzed Differences in the frequency of these complications in childbirth were assessed using Student's test [13]. The statistical probability was indicated by the value of $p > 0.05$. The relative proportions of the indicators by groups were estimated using alternative analysis with the Fisher angular transformation criterion.

For each of the analyzed gestational complications, the relative risk of development was calculated (compared with the control group).

3. Research results

The **Table 1** shows pregnancy outcomes in the surveyed women, taking into account the differences between groups.

Table 1

Pregnancy outcomes

Gestational complication	Main group ($n = 47$)	Comparison group ($n = 45$)	Control group ($n = 45$)
Fetal growth restriction, abs. (%)	4 (8.5)*#	8 (17.8)*	2 (4.4)
Fetal growth restriction up to 30 weeks, abs. (%)	1 (2.1)#	4 (8.9)*	1 (2.2)
Placental dysfunction, abs. (%)	3 (6.4)*#	6 (13.3)*	1 (2.2)
Fetal distress before labor, abs. (%)	4 (8.5)*	5 (11.1)*	1 (2.2)
Fetal distress before labor up to 36 weeks,abs. (%)	1 (2.1)#	4 (8.9)*	–
Fetal distress in childbirth, abs. (%)	5 (10.6)#	11 (24.4)*	3 (6.7)

*Note: * – $p \le 0.05$ when compared with the control group; # – $p \le 0.05$ when compared with the comparison group*

Since the main objective of the study was to prevent fetal growth restriction, the differences between groups in the frequency of this complication were analyzed first of all. The incidence of this complication was significantly higher among women who had a high risk of fetal growth restriction in the first trimester and did not receive the proposed treatment than in the control group and equaled 17.8 % vs. 4.4 % (relative risk – 4.0, confidence interval 95 %). Instead, the appointment of the proposed complex, although did not allow to achieve the level of the control group, but significantly reduced the frequency of fetal growth restriction in the main group to 8.5 % vs. 17.8 % in the comparison group (relative risk 1.9, confidence interval – 95 %).

The difference is more pronounced if we take into account the early detection of fetal growth restriction – up to 30 weeks. If in the comparison group 8.9 % of pregnant women had the development of this complication up to 30 weeks (relative risk 4.0, confidence interval 95 %), the main group on this indicator approached the level of the control group (relative risk 0.957, confidence interval 95 %). It is the early onset of fetal growth restriction that is more significant for perinatal mortality and neonatal morbidity, as it often leads to the need for critical premature birth and the birth of a child with extremely low body weight.

Placental disorders in the form of slowing of blood flow in the umbilical artery were more common in women with identified risk factors (13.3 % in the comparison group vs. 2.2 % in the control group, relative risk 6.0, CI 95 %). In contrast to it, the use of the proposed treatment in women with high risk led to a decrease in this indicator to 6.4 % (relative risk 2.8, CI 95 %).

Fetal distress before childbirth was registered in 5 women (11.1 %) from the high-risk group, which significantly exceeds the control group (relative risk 5.0, CI 95 %). In 4 of 5 women in the comparison group, distress was registered before the onset of gestational maturity of the fetus. In the main group, despite the presence of these risk factors, the use of treatment reduced the over-

all incidence of fetal distress before childbirth (relative risk 3.8, CI 95 %), the maximum was in premature pregnancy up to 2.1 %.

The prescription of a therapeutic complex of drugs has significantly reduced the frequency of fetal distress in childbirth.

4. Discussion

The obtained data indicate that the detection of the risk of fetal growth restriction in the first trimester is not only theoretical but also practical. Since the violation of placental circulation is based on endothelial dysfunction, the appointment of a set of measures to compensate for it – from achieving a favorable ratio of prostacyclin / thromboxane, prevention of excessive activation of the hemostasis system to rational supplementation with micro elements and vitamins has a prophylactic effect.

In most national and international guidelines, the recommended dose of aspirin for the prevention of FGR and fetal malnutrition (FM) in high-risk pregnancies is 100–150 mg [14]. However, the criteria for selecting patients and accurately identifying the risk group for FGR are unclear because, as in most studies of therapy to prevent placental-mediated pregnancy complications, studies have focused more on the treatment of preeclampsia than FGR treatment. This is underscored by the results of a recent large multicenter randomized trial of aspirin to prevent the development of preeclampsia in the early stages. In an evidence-based study of aspirin for the prevention of preeclampsia, a complex algorithm was used to identify high-risk women, including maternal factors, mean blood pressure, pulsation index in uterine artery dopplerometry, values of maternal serum biomarkers (associated with pregnancy maternal plasma protein A and placental growth factor). Although aspirin has been associated with a reduced likelihood of preeclampsia in the early stages, FM values below the 10th, 5th, or 3rd percentiles have remained unchanged [15]. This suggests the need for alternative prognostic models before we can truly assess the effects of aspirin on high-risk groups.

The effect of heparin therapy on uteroplacental circulation is much clearer. In a small open-label study of women with gestational hypertension, LMWH treatment resulted in a decrease in the uterine artery resistance index [16]. However, longer-term use of LMWH in a randomized controlled trial of the effectiveness of LMWH and aspirin against aspirin alone did not reveal differences in the resistance index of the uterine arteries at 22–24 weeks, or in the pulsation index of the umbilical arteries in their doppler studies at 22–24 weeks. [17].

The initial randomized trials of heparin have specifically focused on populations of women with or without thrombophilia because early evidence suggests a relatively strong association between hereditary thrombophilia and the development of preeclampsia and FGR [18]. Recent data from prospective cohort studies suggest that any association with thrombophilia and placental-mediated complications, if any, is only weak [19], so new trials included women regardless of their thrombophilia status. In many studies [20], there are various inclusion criteria that identify women not only at high risk of FGR and preeclampsia, but also previous pregnancy complications, such as habitual miscarriage, and non-placental conditions, such as venous thromboembolism.

The difference between the proposed study from those listed above is the inclusion of micronutrients and vitamins in the therapeutic complex. Modern lifestyle and food stereotypes inherent in women (restriction of consumption of certain foods, vegetarianism, etc.) raise the issue of micronutrient deficiencies much higher than the dietary approach. In addition, the proposed study expanded the approach to assessing the prophylactic effect. Namely, it studied not only the frequency of fetal growth restriction, but other complications associated with endothelial dysfunction, including those that occur in childbirth.

Study limitations. The limitations of this study, in particular the evaluation of its results, are the insufficient statistical sample size and lack of randomization.

Prospect for further research. In the future, the elimination of this limitation is possible in the case of increasing the number of observations, expanding the scope of the study to a multicenter, randomized and placebo-controlled. Such an extension could contribute to the creation of a national protocol for the management of pregnant women with a high risk of placental dysfunction detected in the first trimester.

5. Conclusions

1. Such complications, including placental dysfunction (13.3 % vs. 2.2 %), fetal distress before childbirth (11.1 % vs. 2.2 %) and in childbirth (23.4 % vs. 6.7 %), were much more common among women with an increased risk of fetal growth restriction detected in the first trimester of pregnancy than among healthy pregnant women, which confirms the value of diagnostic criteria for placental dysfunction.

2. Prescribing complex therapy consisting of low doses of aspirin, prophylactic doses of low molecular weight heparin, complex preparation of vitamins and micro elements from the first trimester of pregnancy to women with identified risk factors can reduce the incidence of fetal growth restriction (from 17.8 % without treatment to 8.5 %), placental dysfunction (13, % vs. 6.4 %), fetal distress before childbirth (11.1 % vs. 8.5 %), fetal distress in childbirth (23.4 % vs. 10.6 %).

Conflict of interests

The authors declare that they have no conflicts of interest.

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