DOI: https://doi.org/10.30841/2708-8731.7.2022.272466
UDC: 618.33-007.12-06:616.12-008.331.1-037

Prediction of the development of fetal growth retardation in pregnant women with chronic arterial hypertension

O.V. Deinichenko[1], V.G. Siusiuka[1], Yu.Ya. Krut'[1], M.I. Pavlyuchenko[1], O.D. Kyryliuk[2], N.Yu. Boguslavska[2]
[1]Zaporizhzhia State Medical University
[2]«Regional Perinatal Center» of the Zaporizhzhia Regional Council

During intrauterine life a fetus with growth restriction does hemodynamic, metabolic and hormonal adjustments to cope with the adverse uterine environment, and these changes can become permanent and irreversible. Despite the progress in the knowledge of delayed fetal development, the biomarkers are able to identify this pathology at an early stage and stratify its severity, both before and after childbirth, are still not determined.
The objective: **to evaluate the prognostic value of the angiogenesis marker level, hormonal profile and Doppler examination for fetal growth restriction (FGR) in pregnant women with chronic arterial hypertension (CAH).**
Materials and methods**. A prospective examination of 61 pregnant women with CAH 1-2 degrees was conducted, which included an analysis of the clinical and anamnestic characteristics and the study of the pregnancy course in the first trimester (11-12 weeks). To determine the level of risk factors for the FGR development the examined pregnant women were divided into groups: women with CAH with FGR (n=10), and pregnant women with CAH without FGR (n=51).**
Human chorionic gonadotropin (CHG), progesterone (PG) and estradiol (E) were determined in blood serum. Angiogenesis markers – placental growth factor (P1GF) as a pro-angiogenic factor and soluble fms-like tyrosine kinase (sFlt-1) as an anti-angiogenic factor were studied, the ratio of sFlt-1/PLGF (coefficient K) was calculated.
All patients had Doppler examination of vascular blood flow in the left and right uterine arteries (pulsation index – PI, resistance index – RI and systolic-diastolic ratio – SDR). The ultrasound examination was done with the ultrasound machine "Mylab Six System". Statistical analysis was performed using program Statistica® for Windows 13.0.
A single-factor logistic regression analysis and a method of building logistics regression, which was evaluated by means of receive operating characteristic curve (ROC-curve) according to the area under the curve (AUC) were used to determine the prognostic level of markers, the 95 % confidence interval was calculated.
Results**. In the first trimester of pregnancy in women with CAH the PLGF level was < 8.2 pg/ml (sensitivity – 80.0 %, specificity – 60.78 %), area under the ROC curve (AUC) – 0.697 (95 % CI: 0.566–0.808; p =0.0128), which indicate an increased risk of FGR development. The growth of sFl-1 > 1802.59 ng/ml (sensitivity – 70.0 %, specificity – 64.71 %), area under the ROC-curve (AUC) 0.678 (95 % CI: 0.547–0.792; p=0.05) increase the risk of FGR development. The coefficient K in 11-12 weeks of pregnancy was ≥ 95.36 units (sensitivity – 100.0 %, specificity – 43.14 %), area under ROC-curve (AUC) – 0.735 (95 % CI: 0.607–0.840; p=0.0128), which indicate an increase the risk of FGR development. PG/PlGF ratio is 7.21 (sensitivity – 70.0 %, specificity – 70.59 %) and area under the ROC-curve (AUC) 0.702 (95 % CI: 0.571–0.812; p = 0.0118) also indicate the increase the risk of FGR development, as well as the value of the ratio of E/PLGF > 138.53 (sensitivity – 100.0 %, specificity – 35.29 %) and area under the ROC-curve (AUC) 0.640 (95 % CI: 0.507– 0,759).**
Doppler results in pregnant women with CAH, in the presence of risk factors for FGR development, demonstrate that the CDR was not likely to differ in all groups of patients: 3.62±0.09 units in the persons with CAH and FGR (n=10) and 3.71±0.05 units in the pregnant women with CAG without FGR (n=51) in the right uterine artery; 3.63 ± 0.09 units and 3.71 ± 0.05 units in the left uterine artery, respectively (p<0.05 for all values). However, if PI in the right uterine artery is more than 1.84 units and more than 1.82 units in the left uterine artery, the FGR will further develop.
Conclusions**. According to the results of the study, it was found that pregnant women with CAH 1-2th degrees with FGR development in the future, in the first trimester of gestation (11-12 weeks) have a decrease PlGF level, sFlt-1and the coefficient K increase. These indicators in the 11–12 weeks of pregnancy were: PlGF ≤ 8.2 pg/ml, sFlt-1 > 1802.59 ng/ml, coefficient K ≥ 95.36 units, and PG/PlGF > 7.21 units, E/PlGF > 138.53 units and CHG/PlGF ≥ 30.14 units.**
In the pregnant women with CAG, in whom FGR risk will subsequently determine, the significant changes in the CDR and RI at 11-12 weeks of pregnancy are not established, but with an increase of PI more than 1.84 units in the right uterine artery and more than 1.82 units in the left uterine artery FGR will further develop.
Keywords: *fetal development restriction, angiogenesis factors, hormones, placenta, pregnancy, chronic hypertension.*

Прогнозування розвитку затримки росту плода у вагітних з хронічною артеріальною гіпертензією

О.В. Дейніченко, В.Г. Сюсюка, Ю.Я. Круть, М.І. Павлюченко, Д.О. Кирилюк, Н.Ю. Богуславська

Під час внутрішньоутробного життя плід із затримкою росту здійснює низку гемодинамічних, метаболічних і гормональних коригувань, щоб впоратися з несприятливим середовищем матки, і ці зміни можуть стати постійними та необоротними. Незважаючи на прогрес у знаннях про затримку розвитку плода, біомаркери, здатні ідентифікувати цей стан на ранній стадії та стратифікувати його тяжкість як до, так і після пологів, все ще не визначені.

ISSN 2708-8723 (print)
ISSN 2708-8731 (online)

Мета дослідження: оцінювання прогностичного значення рівня маркерів ангіогенезу, гормонального профілю та допплерографії щодо виникнення затримки розвитку плода (ЗРП) у вагітних із хронічною артеріальною гіпертензією (ХАГ).
Матеріали та методи. Проведено проспективне обстеження 61 вагітної із ХАГ 1–2-го ступеня, яке включало аналіз клініко-анамнестичної характеристики та вивчення особливостей перебігу вагітності у I триместрі (11–12 тиж). Для визначення рівня факторів ризику розвитку ЗРП обстежуваних вагітних було розподілено на групи: жінки з ХАГ, у яких діагностовано ЗРП (n=10), та вагітні з ХАГ без ЗРП (n= 51).
Визначали у сироватці крові хоріонічний гонадотропін людини (human chorionic gonadotropin – CHG), прогестерон (PG), естрадіол (E). Досліджували показники ангіогенезу – плацентарний фактор росту (PlGF) як проангіогенний фактор і плацентарну розчинну fms-подібну тирозинкіназу-1 (sFlt-1) як антиангіогенний фактор, вираховували співвідношення sFlt-1/PlGF (коефіцієнт К).
Усім пацієнткам проводили допплерографію судинного кровотоку у лівій та правій маткових артеріях (індекс пульсації – ІП, індекс резистентності – ІР та систоло-діастолічне співвідношення – СДС). Дослідження виконували на апараті УЗД «MyLab Six System». Статистичний аналіз проводили за допомогою «STATISTICA® for Windows 13.0».
Для визначення прогностичного рівня маркерів застосували однофакторний логістичний регресійний аналіз та метод побудови логістичних моделей регресії, який оцінювали за допомогою кривої операційних характеристик (Receiver Operating Characteristic curve – ROC-кривої) за площею під кривою (Area Under the Curve – AUC), вираховували 95 % довірчий інтервал (ДІ) показників.
Результати. У I триместрі вагітності у жінок із ХАГ PlGF становив < 8,2 пг/мл (чутливість – 80,0 %, специфічність – 60,78 %), площі під кривою ROC (AUC) – 0,697 (95 % ДІ: 0,566–0,808; p=0,0128), що свідчить про підвищений ризик розвитку ЗРП. При збільшенні рівня sFl-1 >1802,59 нг/мл (чутливість – 70,0 %, специфічність – 64,71 %), площі під кривою ROC (AUC) 0,678 (95 % ДІ: 0,547–0,792; p=0,05) ризик розвитку ЗРП зростає. Коефіцієнт К у терміні вагітності 11–12 тиж був ≥ 95,36 од. (чутливість – 100,0 %, специфічність – 43,14 %), площа під ROC-кривою (AUC) – 0,735 (95 % ДІ: 0,607–0,840; p=0,0128), що свідчить про підвищення ризику розвитку ЗРП. Рівень співвідношення PG/PlGF > 7,21 (чутливість – 70,0 %, специфічність – 70,59 %) та площа під кривою ROC (AUC) 0,702 (95 % ДІ: 0,571–0,812; p=0,0118) також вказують на зростання ризику розвитку ЗРП, як і значення співвідношення E/PlGF > 138,53 (чутливість – 100,0 %, специфічність – 35,29 %) та площі під кривою ROC (AUC) на рівні 0,640 (95 % ДІ: 0,507–0,759).
Результати допплерометрії у вагітних із ХАГ за наявності факторів ризику виникнення ЗРП демонструють, що СДС вірогідно не відрізнялося в усіх групах пацієнток: 3,62±0,09 од. у групі з ХАГ та наявністю ЗРП (n=10) та 3,71±0,05 од. у групі вагітних із ХАГ без наявності ЗРП (n=51) у правій матковій артерії; 3,63±0,09 од. та 3,71±0,05 од. відповідно у лівій матковій артерії (p<0,05 для всіх значень). Проте за наявності ІП у правій матковій артерії більше 1,84 од. та більше 1,82 од. у лівій матковій артерії надалі розвиватиметься ЗРП.
Висновки. За результатами дослідження встановлено, що у вагітних із ХАГ 1–2-го ступеня, у яких у подальшому розвивається ЗРП, у I триместрі гестації (11–12 тиж) відзначається зниження рівня PlGF, підвищення sFlt-1 і коефіцієнта К. Зазначені показники в 11–12 тиж вагітності становили: PlGF ≤ 8,2 пг/мл, sFlt-1 > 1802,59 нг/мл, рівень коефіцієнта К ≥ 95,36 од., а співвідношення PG/PlGF > 7,21 од., E/PlGF > 138,53 од. і CHG/PlGF ≥ 30,14 од.
У вагітних із ХАГ, у яких у подальшому буде визначено ризик розвитку ЗРП, суттєвих змін показників СДС та ІР в 11–12 тиж вагітності не спостерігається, проте при зростанні ІП більше 1,84 од. у правій матковій артерій та більше 1,82 од. – у лівій у подальшому розвиватиметься ЗРП.
Ключові слова*: затримка розвитку плода, фактори ангіогенезу, гормони, плацента, вагітність, хронічна артеріальна гіпертензія.*

Cardiovascular diseases have the first place among extragenital diseases in the structure of the causes of perinatal morbidity and mortality. Chronic arterial hypertension (CAH) occupies a leading position among these cardiovascular diseases. CAH promotes the development of long-term vascular and metabolic disorders [5, 25]. It is complicates 1–5% of pregnancies and, compared with the general obstetrical population, it is associated with higher rates of adverse maternal and perinatal outcomes [5, 11, 19]. Item, chronic hypertension in pregnancy is associated with a host of adverse outcomes that include preeclampsia, cesarean delivery, cerebrovascular accidents, fetal growth restriction, preterm birth, and maternal and perinatal death [3, 10, 11, 14, 27].

There is a decrease in placental blood flow in pregnant women with CAH due to changes in the functioning of the cardiovascular system. Disturbances of the normal relationship between vasodilators and vasoconstrictors in pregnant women with CAH are accompanied by dysregulation of vascular tone and leads to placental insufficiency [22, 23]. One of the leading theories of placental insufficiency is vascular-endothelial dysfunction theory. Endothelial cells of vessels synthesize a large number of biologically active substances that are involved in providing a variety of processes in the physiological and pathological gestational processes [2, 4, 6, 24].

Preeclampsia complicates approximately 20% of pregnancies in women with chronic hypertension and is associated with increased maternal and perinatal morbidity compared with preeclampsia alone. A characteristic feature of both preeclampsia and chronic hypertension is a systemic inflammatory response that causes or exacerbates endothelial dysfunction [15]. Fetal growth restriction (FGR) is observed in 10–15 % of pregnancies and is frequently seen in association with other pregnancy complications, such as CAH and preeclampsia [7]. About 80% of cases remain undetected [16, 26]. Recognizing intrauterine growth restriction is a matter of great concern because this condition can significantly affect the newborns short- and long-term health. During intrauterine life, the growth-restricted fetus makes a number of hemodynamic, metabolic, and hormonal adjustments to cope with the adverse uterine environment, and these changes may become permanent and irreversible. Despite advances in our knowledge of FGR newborns, biomarkers capable of identifying this condition early on, and stratifying its severity both pre- and postnatally, are still lacking [1, 16, 18, 20].

The activity of placental angiogenesis is controlled by a spectrum of growth factors with pro-angiogenic and

ISSN 2708-8723 (print)
ISSN 2708-8731 (online)

anti-angiogenic properties. The placental growth factor (PlGF) in the first trimester of pregnancy stimulates the synthesis of trophoblastic DNA, increases the number of trophoblast cells and improves the conditions for its infestation. During the third trimester of pregnancy PlGF expression reaches a maximum of 28-30 weeks of gestation, gradually increasing from the first to the second trimester of pregnancy [12, 21, 28]. Anti-angiogenic factors include placental soluble fms-like tyrosine kinase (sFlt-1). It counteracts the action of PlGF on specific receptors [17]. The imbalance between pro- and anti-angiogenic factors contributes to placental insufficiency [13]. Thus, according to the results of our previous studies, it was established that in the first trimester of pregnancy (11-12 weeks of gestation) in women with CAH, a shift in the balance between pro- and antiangiogenic factors is determined [8, 9].

The role of the factors of angiogenesis and hormones of pregnancyin pregnant women with hypertension has been studied inadequately and their interaction in such patients is not fully elucidated at present time.

MATERIALS AND METHODS

Criteria for inclusion in the study: pregnancy, the presence of CAH of 1-2 grades. Criteria for exclusion from the study: CAH of 3 grade, diabetes mellitus, multiple pregnancy, chromosomal and genetic disorders, thrombophilia, perinatal infections, systemic connective tissue diseases, heart disease (heart`s defects, myocarditis), anemia of moderate to severe degrees, diseases of the lungs, oncological diseases, pregnancy that comes with assisted reproductive technology.

Conducting a prospective study of 61 pregnant women, which included: analysis of clinical and anamnestic characteristics and study of the peculiarities of pregnancy in women with chronic hypertension in the first trimester of pregnancy (11-12 weeks). In the dynamics of pregnancy, all patients were examined by a physician. According to the indications of pregnant women, consultations of specialists of other specialties were carried out and additional instrumental research methods were performed.

The open prospective controlled study involved 61 pregnant women with CAH 1-2 degrees. In order to determine the level of risk factors for the development of FGR, the studied pregnant women were divided into groups: women with CAH who were diagnosed with FGR (n=10) and pregnant women with CAH who did not have FGR (n=51).

Anamnesis, general clinical examination, measured of blood pressure, standard obstetric and gynecological examination according to clinical protocols were done in all cases. The evaluation of the outcome of the accouchement was performed on the assessment of the fetal condition on the Apgar scale, weight of the fetus. AH was diagnosed according to the existing clinical protocols.

The following hormones were determined: CHG, PG, E. Among the angiogenesis indices, the placental growth factor (PGF), as a pro-angiogenic factor and placental soluble fms-like tyrosine kinase (sFlt-1) was determined as an anti-angiogenic factor, sFlt-1/PGF ratio was also estimated. Research of hormones and factors of angiogenesis was performed on the basis of the Educational Medical Laboratory Center (the head is professor A. V. Abramov) of the Zaporizhzhya State Medical University. For this purpose, the full-wave enzyme-linked enzyme analyzer Sirio-S (Seac, Italy) was used. Indicators of hormones and factors of angiogenesis were performed using immuno-enzymatic methods in accordance with the relevant instructions using the appropriate sets of reagents: CHG, PG, E (Monobind Inc, USA); PGF and sFlt-1 (R&D systems, Inc, USA&Canada). All patients underwent Doppler vascular blood flow, blood flow parameters in the left and right uterine arteries were determined (pulsatility index (PI), resistance index (IR) and systolic-diastolic ratio (SDR)). PI shows a linear correlation of vascular resistance, SDR and IP show a parabolic relationship with an increase in vascular resistance. The research was carried out on the "MyLab Six System" ultrasound machine. The research was carried out in the morning. The examination technique was carried out according to the practical recommendations of the ISUOG using Doppler sonography in obstetrics.

Statistical analysis was done by using «STATISTICA® for Windows 13.0». Normality of data`s distribution in groups was determined by Shapiro-Wilk method. Results were presented as mean ± error of mean (M ± m). Differences between groups were estimated by Student's criterion. To determine the relationship between the indicators, the correlation coefficient was calculated using the Spirmen method; statistically significant results were considered with a coefficient of more than 0,3 and with a level of $p < 0,05$.

RESULTS AND DISCUSSION

In order to determine the level of risk factors for the development of FGR, the studied pregnant women were divided into groups: women with CAH who were diagnosed with FGR (n=10) and pregnant women with CAH who did not have FGR (n=51).

As a risk factors for the development of FGR in pregnant with CAH, we considered levels of PlGF, sFlt-1, sFlt-1/PlGF (coefficient K), PIr, PIl, indicators of progesterone to placental growth factor (PG/PlGF), estradiol to placental factor growth (E/PlGF) and human chorionic gonadotropin to placental growth factor (CHL/PlGF).

The characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR are given in table 1.

ROC-analysis with the construction of a characteristic curve (ROCcurve, receiver operator characteristic curve) was used to identify the prognostically optimal point of distribution of the level of biomarkers (optimal ratio of sensitivity and specificity).

According to univariate logistic regression analysis and ROC analysis, the level of PlGF in the 11–12 weeks

Table 1

Characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR, n (%)

Indicator	Pregnant women with CAH and FGR (n=10)	Pregnant women with CAH, without FGR (n=51)	Probability, p
PlGF, n (%)	8 (80,0)	20 (39,2)	< 0,01
sFlt-1, n (%)	7 (70,0)	19 (37,3)	< 0,05
K, n (%)	10 (100)	30 (58,8)	< 0,01

ISSN 2708-8723 (print)
ISSN 2708-8731 (online)

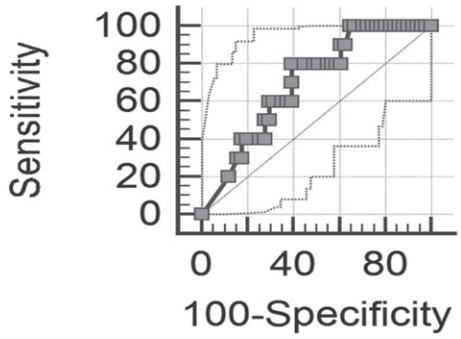

Fig. 1. ROC-curve for the level of PlGF in pregnant women with CAH at 11-12 weeks of pregnancy in relation to the development of FGR

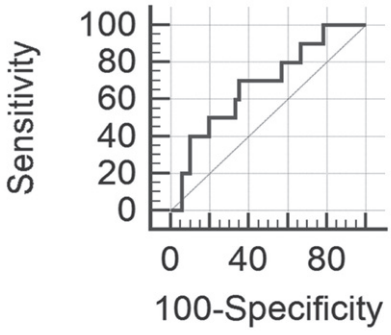

Fig. 2. ROC-curve for the level of sFlt-1 in pregnant women with CAH at 11–12 weeks of pregnancy in relation to the development of FGR

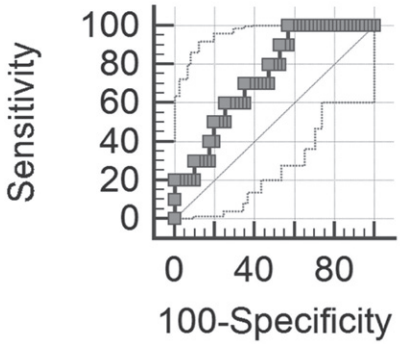

Fig. 3. ROC curve for the level of K in pregnant women with CAH at 11–12 weeks' gestation in relation to the development of FGR

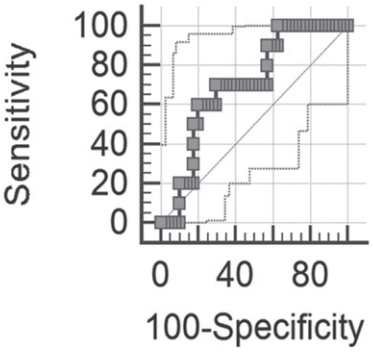

Fig. 4. ROC-curve for the level of the PG/PlGF ratio in pregnant women with CAH at 11–12 weeks of pregnancy in relation to the development of FGR

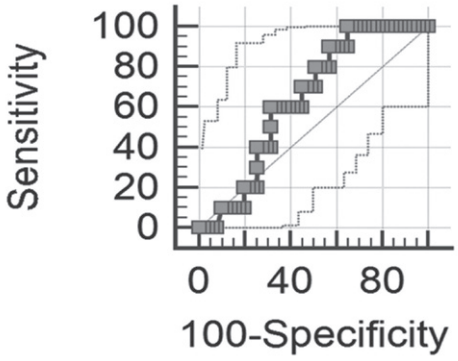

Fig. 5. ROC-curve for the level of the E/PlGF ratio in pregnant women with CAH at 11–12 weeks of pregnancy in relation to the development of FGR

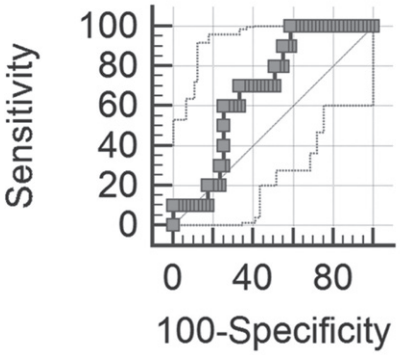

Fig. 6. ROC-curve for the level of the CHG/PlGF ratio in pregnant women with CAH at 11–12 weeks' gestation in relation to the development of FGR

of pregnancy < 8.12 pg/ml (sensitivity 80.0%, specificity 60.78%), the area under the ROC curve (AUC) 0.697 (CI 0.566–0.808; p=0.0128) increases the risk of developing FGR (Fig. 1).

With an increase in the level of sFlt-1 > 1802.59 ng/ml (sensitivity 70.0%, specificity 64.71%), the area under the ROC curve (AUC) 0.678 (CI 0.547–0.792; p=0.05), the risk of developing FGR increases (Fig. 2).

According to the data of the conducted research, the level of the coefficient K ≥ 95.36 units in the period of pregnancy of 11–12 weeks (sensitivity 100.0%, specificity 43.14%), the area under the ROC-curve (AUC) 0.735 (CI 0.607–0.840; p=0.0128) increases the risk of the development of FGR (Fig. 3).

During examining the parameters of the hormonal profile, there was no statistically significant difference between the groups of patients (p>0.05 for all values). However, the ratio of the level of hormone indicators to the placental growth factor increases the sensitivity of these indicators for predicting the occurrence of FGR in these groups of

Table 2

Characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR, n (%)

Indicator	Pregnant women with CAH and FGR (n=10)	Pregnant women with CAH, without FGR (n=51)	Probability, p
PG/PlGF, n (%)	7 (70,0)	17 (33,3%)	< 0,03
E/PlGF, n (%)	10 (100%)	33 (64,7%)	< 0,01
CHG/PlGF, n (%)	10 (100%)	31 (60,8%)	< 0,01

Table 3

Characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR according to Doppler, n (%)

Indicator	Pregnant women with CAH and FGR (n=10)	Pregnant women with CAH, without FGR (n=51)	Probability, p
PIr, n (%)	6 (60,0)	5 (9,8)	0,0001
PIl, n (%)	7 (70,0)	4 (7,8)	0,0001

pregnant women ($p<0.05$). The characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR are shown in table 6.2.

If the level of PG/PlGF ratio increases > 7.21 (sensitivity 70.0%, specificity 70.59%), the area under the ROC curve (AUC) 0.702 (CI 0.571–0.812; p=0.0118), the risk increases development of FGR (Fig. 4).

When studying the indicators of the E/PlGF ratio, at levels > 138.53 (sensitivity 100.0%, specificity 35.29%), the area under the ROC curve (AUC) 0.640 (CI 0.507–0.759), the risk of development of FGR increases (Fig. 5).

According to the data of the conducted study, at 11–12 weeks of pregnancy, the level of the CHG/PlGF ratio ≥ 30.14 (sensitivity 100.0%, specificity 41.8%), the area under the ROC curve (AUC) 0.684 (CI 0.553–0.797; p=0.0154) increases the risk of the development of FGR (Fig. 6).

Thus, in pregnant women with CAH 1 and 2 degrees, who later develop FGR, in the first trimester of pregnancy (11–12 weeks of gestation), a decrease in PlGF levels is determined, and an increase in sFlt-1 and K levels.

The levels of the hormonal profile in this pathology do not differ statistically significantly (p>0.05), but when determining the ratio of hormone indicators to the placental growth factor, an increase in levels is observed, therefore, determining the ratio of these indicators can be a prognostic marker for the occurrence of FGR in pregnant women with CAH.

Thus, in pregnant women with CAH of the 1st and 2nd degrees, in whom the FGR will be determined in the future, at 11-12 weeks of gestation, the levels of PlGF reach values ≤ 8.2 pg/ml, the value of sFlt-1 reaches > 1802.59 ng/ml, the level coefficient K ≥ 95.36 units, the level of PG/PlGF ratios > 7.21 units, E/PlGF > 138.53 units, CHG/PlGF ≥ 30.14 units.

Then, the prognostic value of dopplerometry indicators in pregnant women with chronic arterial hypertension regarding the development of fetal growth retardation was carried out. The levels of PIp, PIl, SDRr, SDRl, and indicators of IRr and IRl were considered as risk factors for the development of FGR in pregnant women with CAH when performing dopplerometry in the left and right uterine arteries. The characteristics of pregnant women with CAH according to the presence of risk factors for the occurrence of FGR are shown in table 3.

SDR was not significantly different in all groups of patients: 3.62 ± 0.09 units. in the group with CAH and the presence of FGR (n=10), 3.71 ± 0.05 units. in the group of pregnant women with CAH without the presence of FGR (n=51) for SDRr; 3.63 ± 0.09 units, 3.71 ± 0.05 units, respectively, for SDRl, p>0.05 for all values.

IR indicators also did not differ significantly in all groups of patients: 0.77 ± 0.03 units. in the group of CAH with FGR and , 0.74 ± 0.03 units. in the group with CAH without FGR, for IRr; 0.77 ± 0.03 units, 0.73 ± 0.02 units, respectively, for IRl, p>0.05 for all values.

PIp and PIl were significantly higher than the values in women with CAH, who developed FGR: 1.89 ± 0.04 units. and 1.89 ± 0.03 units, respectively, against 1.71 ± 0.02 units. in the group without FGR, p<0.001 for all values.

According to the data of univariate logistic regression analysis and ROC analysis, the level of PIr when conducting dopplerometry at 11–12 weeks of pregnancy > 1.84 (sensitivity 60.0%, specificity 92.16%), the area under the ROC curve (AUC) 0.788 (CI 0.655–0.882; p=0.0023) increases the risk of developing FGR (Fig. 7).

With an increase in the level of PIl > 1.82 (sensitivity 70.0%, specificity 94.12%), the area under the ROC curve (AUC) 0.796 (CI 0.673–0.888; p=0.0041), the risk of developing FGR increases (Fig. 8).

Thus, there are no reliable changes in SDR and IR indicators at 11–12 weeks of pregnancy in pregnant women with CAH with the development of FGR in the future.

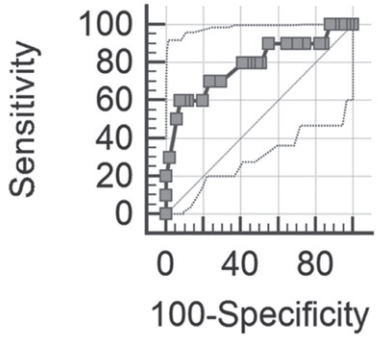

Fig. 7. ROC-curve for the level of PIr in pregnant women with CAH at 11–12 weeks of pregnancy in relation to the development of FGR

REPRODUCTIVE HEALTH OF WOMAN
РЕПРОДУКТИВНЕ ЗДОРОВ'Я ЖІНКИ
№7 (62)/2022
ISSN 2708-8723 (print)
ISSN 2708-8731 (online)

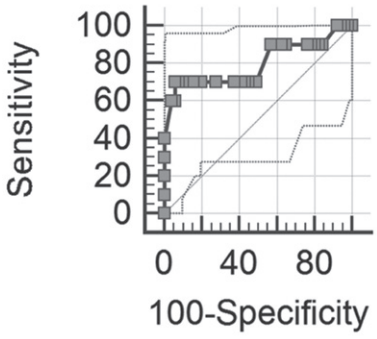

Fig. 8. ROC-curve for the level of PII in pregnant women with CAH at 11–12 weeks of pregnancy in relation to the development of FGR

In pregnant women with CAH of the 1st or 2nd degree, when the PIr indicator exceeds 1.84 units. (≥1.84 units) and PIl over 1.82 units. (≥1.84 units) at 11–12 weeks of pregnancy, FGR will develop in the future.

CONCLUSIONS

According to the results of the study, it was established that in pregnant women with CAH of the 1st and 2nd degrees, who later develop FGR, in the first trimester of pregnancy (11–12 weeks of gestation), a decrease in PlGF levels is determined, and an increase in sFlt-1 and K. The indicated indicators on 11–12 weeks of gestation, there were: PlGF ≤ 8.2 pg/ml, sFlt-1 > 1802.59 ng/ml, level of coefficient K ≥ 95.36 units. ratios of PG/PlGF > 7.21 units, E/PlGF > 138.53 units. and CHG/PlGF ≥ 30.14 units.

Also, according to the results of the study, it was established that in pregnant women with CAH, in whom the risk of developing FGR will be determined in the future, there are no significant changes in indicators of SDR and IR at 11–12 weeks of pregnancy in pregnant women with CAH with the development of FGR in the future. However, in pregnant women with CAH of the 1st or 2nd degree, when the PIr indicator exceeds 1.84 units (≥1.84 units) and PIl over 1.82 units (≥1.84 units) at 11–12 weeks of pregnancy, FGR will develop in the future.

The levels of the hormonal profile in this pathology do not differ statistically significantly (p>0.05), but when determining the ratio of hormone indicators to the placental growth factor, an increase in levels is observed, therefore, determining the ratio of these indicators can be a prognostic marker for the occurrence of FGR in pregnant women with CAH.

Conflict of interests. Absent.

Information about the authors

Deinichenko Olena V. – MD, PhD, Assistant of Professor, Department of Obstetrics and Gynecology, Zaporizhzhia State Medical University. *E-mail: agol0309@gmail.com*
ORCID: 0000-0002-8932-230X

Siusiuka Volodymyr G. – MD, PhD, DSc, Associate Professor, Department of Obstetrics and Gynecology, Zaporizhzhia State Medical University. E-mail: svg.zp.ua@gmail.com
ORCID: 0000-0002-3183-4556

Krut' Yurii Ya. – MD, PhD, DSc, Professor, Head of the Department of Obstetrics and Gynecology, Zaporizhzhia State Medical University. *E-mail: yuriy.krut@ukr.net*
ORCID: 0000-0002-0501-6752

Pavlyuchenko Mykhailo I. – MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Zaporizhzhia State Medical University *E-mail: dr_pavl@ukr.net*
ORCID: 0000-0002-9235-0205

Kyryliuk Oleksandr D. – MD, PhD, Director, Municipal Non-profit Enterprise «Regional Perinatal Center», Zaporizhzhia regional council. *E-mail: rdom5@i.ua*
ORCID: 0000-0002-0173-5661

Bohuslavska Natalia Y. – MD, Director's Assistant, Municipal Non-profit Enterprise «Regional Perinatal Center», Zaporizhzhia regional council. *E-mail: bohuslavska@i.ua*
ORCID: 0000-0001-5401-3999

Відомості про авторів

Дейніченко Олена Валеріївна – д-р філософії, асистентка, кафедра акушерства і гінекології, Запорізький державний медичний університет. *E-mail: agol0309@gmail.com*
ORCID: 0000-0002-8932-230X

Сюсюка Володимир Григорович – д-р мед. наук, доцент, кафедра акушерства і гінекології, Запорізький державний медичний університет. *E-mail: svg.zp.ua@gmail.com*
ORCID: 0000-0002-3183-4556

Круть Юрій Якович – д-р мед. наук, проф., завідувач, кафедра акушерства і гінекології, Запорізький державний медичний університет. *E-mail: yuriy.krut@ukr.net*
ORCID: 0000-0002-0501-6752

Павлюченко Михайло Іванович – канд. мед. наук, доцент, кафедра акушерства і гінекології, Запорізький державний медичний університет. *E-mail: dr_pavl@ukr.net*
ORCID: 0000-0002-9235-0205

Кирилюк Олександр Дмитрович – канд. мед. наук, директор, комунальне некомерційне підприємство «Обласний перинатальний центр», Запорізька обласна рада. *E-mail: rdom5@i.ua*
ORCID: 0000-0002-0173-5661

Богуславська Наталія Юріївна – канд. мед. наук, заступниця директора, комунальне некомерційне підприємство «Обласний перинатальний центр», Запорізька обласна рада. *E-mail: bohuslavska@i.ua*
ORCID: 0000-0001-5401-3999

REFERENCES

1. Armengaud JB, Yzydorczyk C, Siddeek B, Peyter AC, Simeoni U. Intrauterine growth restriction: clinical consequences on health and disease at adulthood. Reprod Toxicol. 2021;99:168-76. doi: 10.1016/j.reprotox.2020.10.005.
2. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol. 2018;49:53-65. doi: 10.1016/j.bpobgyn.2018.02.009.
3. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol. 2020;222(6):532-41. 10.1161/CIRCULATIONAHA.113.003904.
4. Bontsevich RA, Severinova OV, Chukhareva NA, Filinichenko TS, Gavrilova AA. The successful clinical case of a severe arterial hypertension management during preconception and pregnancy. Indo Am J Pharm Sci. 2018;5(10):10396-400.
5. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014;348:g2301. doi: 10.1136/bmj.g2301.
6. Bruin C, Damhuis S, Gordijn S, Ganzevoort W. Evaluation and Management of Suspected Fetal Growth Restriction. Obstet Gynecol Clin North Am. 2021;48(2):371-85. doi: 10.1016/j.ogc.2021.02.007.
7. Colson A, Sonveaux P, Debi ve F, Sferruzzi-Perri AN. Adaptations of the human placenta to hypoxia: opportunities for interventions in fetal growth restriction. Hum Reprod Update. 2021;27(3):531-69. doi: 10.1093/humupd/dmaa053
8. Deinichenko O, Krut Yu, Siusiuka V, Pavlyuchenko M. Indicators of angiogenesis in pregnant women with arterial hypertension. Grail of science. 2022;20:160-3.
9. Deinichenko OV, Siusiuka VG, Krut' YuYa, Gaidai NV, Pavlyuchenko MI, Puchkov VA, Bohomolova OA. Indicators of angiogenesis and hormonal profile in pregnant women with chronic hypertension in the first trimester. Reprod Health Woman. 2022;58(3):34-9.
10. Delker E, Bandoli G, LaCoursiere Y, Ferran K, Gallo L, et al. Chronic hypertension and risk of preterm delivery: National Longitudinal Study of Adolescents to Adult Health. Paediatr Perinat Epidemiol. 2022;36(3):370-9. doi: 10.1111/ppe.12858.
11. Dumitrascu-Biris D, Nzelu D, Dassios T, Nicolaides K, Kametas NA. Chronic hypertension in pregnancy stratified by first-trimester blood pressure control and adverse perinatal outcomes: A prospective observational study. Acta Obstet Gynecol Scand. 2021;100(7):1297-304. doi: 10.1111/aogs.14132.
12. Farina A, Curti A, Youssef A, Rapacchia G, Righetti F, Simonazzi G, Bernabini D, Rizzo N. Uterine artery Doppler and biochemical markers (PAPP-A, PlGF, sFlt-1, P-selectin, NGAL) at 11 + 0 to 13 + 6 weeks in the prediction of late (>34 weeks) pre-eclampsia. Prenatal diAHnosis. 2011;31(12):1141-6. doi: 10.1002/pd.2848.
13. Gaccioli F, Aye ILMH, Sovio U, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. Am J Obstet Gynecol. 2018;218(2S):725-37. doi: 10.1016/j.ajog.2017.12.002.
14. Greenberg VR, Silasi M, Lundsberg LS, Culhane JF, Reddy UM, Partridge C, Lipkind HS. Perinatal outcomes in women with elevated blood pressure and stage 1 hypertension. Am J Obstet Gynecol. 2021;224(5):521.e1-521.e11. doi: 10.1016/j.ajog.2020.10.049.
15. Kametas NA, Nzelu D, Nicolaides KH. Chronic hypertension and superimposed preeclampsia: screening and diagnosis. Am J Obstet Gynecol. 2022;226(2S):1182-95. doi: 10.1016/j.ajog.2020.11.029.
16. Kolokot NH. Improvement of diagnosis of fetal growth retardation in pregnant women by using biochemical markers characterizing disorders of stress adaptation. Zaporizhzhya Med J. 2018;20(2):231-5.
17. Kumar M, Sharma K, Singh R, Singh S, Ravi V, Singh K, Gupta U, Bhattacharya J. Role of maternal factors, PAPP-A, and Doppler in screening for early- and late-onset pregnancy hypertension in Asian population. Hypertension in pregnancy. 2016;35(3):382-393. doi: 10.3109/10641955.2016.1161766.
18. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (International Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152(1):3-57. doi: 10.1002/ijgo.13522.
19. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2017;50(2):228-35. doi: 10.1002/uog.17493.
20. Priante E, Verlato G, Giordano G, Stocchero M, Visentin S, Mardegan V, Baraldi E. Intrauterine Growth Restriction: New Insight from the Metabolomic Approach. Metabolites. 2019;9(11):267. doi: 10.3390/metabo9110267.
21. Rizzo G, Mappa I, Bitsadze V, S odki M, Khizroeva J, Makatsariya A, D'Antonio F. Role of Doppler ultrasound at time of diagnosis of late-onset fetal growth restriction in predicting adverse perinatal outcome: prospective cohort study. Ultrasound Obstet Gynecol. 2020;55(6):793-98. doi: 10.1002/uog.20406.
22. Roos-Hesselink J, Baris L, Johnson M, De Backer J, Otto C, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry of Pregnancy and Cardiac Disease (ROPAC). J Eur Heart J. 2019;40(47):3848-55. doi: 10.1093/eurheartj/ehz136.
23. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130(12):1003-08. doi: 10.1161/CIRCULATIONAHA.114.009029.
24. Stepan H, Hund M, Andraczek T. Combining biomarkers to predict pregnancy complications and redefine preeclampsia the angiogenic-placental syndrome. Hypertension. 2020;75(4):918-26. doi: 10.1161/HYPERTENSIONAHA.119.13763.
25. Thompson LP, Pence L, Pinkas G, Song H, Telugu BP. Placental hypoxia during early pregnancy causes maternal hypertension and placental insufficiency in the hypoxic guinea pig model. Biol Reprod. 2016;95(6):128. doi: 10.1095/biolreprod.116.142273.
26. Tong S, Kaitu-Lino TJ, Walker SP, MacDonald TM. Blood-based biomarkers in the maternal circulation associated with fetal growth restriction. Prenat Diagn. 2019;39(11):947-57. doi: 10.1002/pd.5525.
27. Tsakiridis I, Giouleka S, Arvanitaki A, Mamopoulos A, Giannakoulas G, Papazisis G, et al. Chronic hypertension in pregnancy: synthesis of influential guidelines. J Perinat Med. 2021;49(7):859-72. doi: 10.1515/jpm-2021-0015.
28. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstr m M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13-22. doi: 10.1056/NEJMoa1414838.

Стаття надійшла до редакції 21.09.2022. – Дата першого рішення 27.09.2022. – Стаття подана до друку 08.11.2022

ISSN 2708-8723 (print)
ISSN 2708-8731 (online)