

# Indicators of angiogenesis and hormonal profile in pregnant women with chronic hypertension in the first trimester

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The role of angiogenesis factors and hormonal profile in pregnant women with arterial hypertension has not been detailed studied, and their interaction in such patients has not been determined at present time.

*The objective:* to determine the features of angiogenesis factors and hormonal profile in pregnant women with arterial hypertension of the 1 and 2 grade.

*Materials and methods.* A prospective study was conducted in 88 pregnant women, which included: analysis of clinical and anamnestic characteristics and the study of pregnancy characteristics in women with chronic arterial hypertension (CAH) in the I trimester of pregnancy (11–12 weeks). The open prospective controlled study involved 61 pregnant women with CAH of the 1 and 2 stages which consisted the main group. The control group included 27 healthy pregnant women with physiological pregnancy.

Concentrations of human chorionic gonadotropin (hCG), progesterone (PG), estradiol (E) and markers of angiogenesis – placental growth factor (PIGF) as a proangiogenic factor and soluble fms-like tyrosine kinase (sFlt-1) as an antiangiogenic factor were determined in the blood serum of all patients, sFlt-1/PIGF ratio was also estimated (K). Statistical analysis was performed using «STATISTICA® for Windows 13.0».

*Results.* In the I trimester of pregnancy in women with CAH, a shift in the balance between pro- and anti-angiogenic factors is determined, which is manifested by a statistically significant ( $p < 0.05$ ) increase sFlt-1 level (1700.9 pg/ml) and a decrease PIGF level in 3.7 times (9.1 pg/ml) and, accordingly, an increase K coefficient (sFlt-1/PIGF) by 5.3 times (184.5). The mean concentrations of E, PG and hCG in pregnant women of the main group did not differ statistically significantly from those in the control group. However, according to the results of the correlation analysis, PIGF and PG indicators have feedback in pregnant women with CAH ( $r = -0.29$ ;  $p < 0.05$ ).

When calculating the correlation of PIGF and hormones, it was found that in pregnant women with CAH there is their growth according to the control group, namely the indicator hCG correlates with PIGF (51.8 units vs. 14.8 units) 3.5 times, E correlates with PIGF (309.7 units vs. 70.0 units) 4.4 times and PG correlates with PIGF (4.8 units vs. 1.0 units) 4.8 times ( $p < 0.001$  for all indicators). These changes indicate the presence of angiogenesis disorders in pregnant women with chronic hypertension, starting from the I trimester of gestation.

*Conclusions.* Pregnant women with CAH in the I trimester have disturbances in balance between pro-angiogenic and anti-angiogenic factors with prevalence of sFlt-1 and decrease of PIGF in blood serum. Because of such imbalance in pregnant women with CAH of the 1 and 2 grade, the interaction of angiogenesis factors and hormones changed from direct to inverse. It may lead to the development of placental dysfunction in the future, so treatment and prevention should be provided for the pregnant women with CAH in the I trimester.

*Keywords:* angiogenesis factors, placenta, hormones, pregnancy, hypertension.

## Показники ангіогенезу та гормонального профілю у вагітних з хронічною артеріальною гіпертензією у I триместрі

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Роль факторів ангіогенезу та гормонального профілю у вагітних з артеріальною гіпертензією вивчена недостатньо і їхня взаємодія у таких пацієнтів на сьогодні не з'ясована.

*Мета дослідження:* встановлення особливостей факторів ангіогенезу та гормонального профілю у вагітних з артеріальною гіпертензією 1-го та 2-го ступеня.

*Матеріали та методи.* Проведено проспективне дослідження у 88 вагітних, яке включало: аналіз клініко-анамнестичної характеристики та вивчення особливостей вагітності у жінок із хронічною артеріальною гіпертензією (ХАГ) у I триместрі гестації (11–12 тиж). У відкритому проспективному контрольованому дослідженні брали участь 61 вагітна з ХАГ 1-го та 2-го ступеня, які увійшли до основної групи. До контрольної групи увійшли 27 вагітних із фізіологічним перебігом вагітності.

Усім пацієнткам визначали у сироватці крові концентрації хоріонічного гонадотропіну (ХГТ), прогестерону (ПГ), естрадіолу (Е) та маркери ангіогенезу – фактор росту плаценти (PIGF) як проангіогенний фактор і розчинну fms-подібну тирозинкіназу (sFlt-1) як антиангіогенний фактор, також оцінювали співвідношення (К) sFlt-1/PIGF. Статистичний аналіз проводили за допомогою «STATISTICA® for Windows 13.0».

**Результати.** У І триместрі вагітності у жінок із ХАГ визначається зсув балансу між про- та антиангіогенними факторами, що проявляється статистично значущим ( $p < 0,05$ ) підвищенням рівня sFlt-1 (1700,9 пг/мл) і зниженням рівня PlGF у 3,7 раза (9,1 пг/мл) та відповідно підвищенням коефіцієнта К (sFlt-1/PlGF) у 5,3 раза (184,5). Середні значення концентрації Е, ПГ та ХГТ у вагітних основної групи статистично значуще не відрізнялися від таких у контрольній групі. Однак за результатами кореляційного аналізу показники PlGF і ПГ мають зворотний зв'язок у вагітних із ХАГ ( $r = -0,29$ ;  $p < 0,05$ ).

При розрахунку кореляції PlGF і гормонів було виявлено, що у вагітних із ХАГ спостерігається зростання їхніх значень у контрольній групі, а саме – показник ХГТ корелює з PlGF (51,8 од. проти 14,8 од.) у 3,5 раза, Е корелює з PlGF (309,7 од. проти 70,0 од.) у 4,4 раза, а ПГ корелює з PlGF (4,8 од. проти 1,0 од.) у 4,8 раза ( $p < 0,001$  для всіх показників). Ці зміни свідчать про наявність порушень ангиогенезу у вагітних із ХАГ, починаючи з І триместра вагітності.

**Висновки.** У вагітних із ХАГ у І триместрі спостерігається порушення балансу між проангіогенними та антиангіогенними факторами з переважанням sFlt-1 та зниженням PlGF у сироватці крові. Через такий дисбаланс у вагітних із ХАГ 1-го та 2-го ступенів взаємодія факторів ангиогенезу та гормонів змінилася з прямої на зворотну. Надалі це може призвести до розвитку плацентарної дисфункції, тому лікування та профілактику слід проводити вагітним із ХАГ у І триместрі.

**Ключові слова:** фактори ангиогенезу, плацента, гормони, вагітність, гіпертензія.

## Показатели ангиогенеза и гормонального профиля у беременных с хронической артериальной гипертензией в I триместре

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Роль факторов ангиогенеза и гормонального профиля у беременных с артериальной гипертензией изучена недостаточной и их взаимодействие у таких пациентов на сегодня не установлено.

**Цель исследования:** установление особенностей факторов ангиогенеза и гормонального профиля у беременных с артериальной гипертензией 1-й и 2-й степени.

**Материалы и методы.** Проведено проспективное исследование у 88 беременных, которое включало: анализ клинико-анамнестической характеристики и изучение особенностей беременности у женщин с хронической артериальной гипертензией (ХАГ) в I триместре беременности (11–12 нед). В открытом проспективном контролируемом исследовании участвовала 61 беременная с ХАГ 1-й и 2-й степени, которые вошли в основную группу. В контрольную группу вошли 27 беременных с физиологическим течением беременности.

Всем пациенткам определяли в сыворотке крови концентрации хорионического гонадотропина (ХГТ), прогестерона (ПГ), эстрадиола (Э) и маркеры ангиогенеза – фактор роста плаценты (PlGF) как проангиогенный фактор и растворимую fms-подобную тирозинкиназу (sFlt-1) как антиангиоген, также оценивали соотношение (К) sFlt-1/PlGF. Статистический анализ проводили с помощью «STATISTICA® for Windows 13.0».

**Результаты.** В I триместре беременности у женщин с ХАГ определяется смещение баланса между про- и антиангиогенными факторами, что проявляется статистически значимым ( $p < 0,05$ ) повышением уровня sFlt-1 (1700,9 пг/мл) и снижением уровня PlGF в 3,7 раза (9,1 пг/мл) и соответственно повышением коэффициента К (sFlt-1/PlGF) в 5,3 раза (184,5). Средние значения концентрации Э, ПГ и ХГТ у беременных в основной группе статистически значимо не отличались от таковых в контрольной группе. Однако по результатам корреляционного анализа показатели PlGF и ПГ имеют обратную связь у беременных с ХАГ ( $r = -0,29$ ;  $p < 0,05$ ).

При расчете корреляции PlGF и гормонов было обнаружено, что у беременных с ХАГ наблюдается рост их значений в контрольной группе, а именно – показатель ХГТ коррелирует с PlGF (51,8 ед. против 14,8 ед.) в 3,5 раза, Э коррелирует с PlGF (309,7 ед. против 70,0 ед.) в 4,4 раза, а ПГ коррелирует с PlGF (4,8 ед. против 1,0 ед.) в 4,8 раза ( $p < 0,001$  для всех показателей). Эти изменения указывают на наличие нарушений ангиогенеза у беременных с ХАГ, начиная с I триместра беременности.

**Выводы.** У беременных с ХАГ в I триместре наблюдается нарушение баланса между проангиогенными и антиангиогенными факторами с преобладанием sFlt-1 и снижением PlGF в сыворотке крови. Из-за такого дисбаланса у беременных с ХАГ 1-й и 2-й степени взаимодействие факторов ангиогенеза и гормонов изменилось с прямого на обратное. В дальнейшем это может привести к развитию плацентарной дисфункции, поэтому лечение и профилактику следует проводить беременным с ХАГ в I триместре.

**Ключевые слова:** факторы ангиогенеза, плацента, гормоны, беременность, гипертензия.

Cardiovascular diseases complicates between 1% and 4% of pregnancies, and accounts for up to 15% of maternal deaths [1, 2]. According to the most recent statistics from the World Health Organization (WHO), maternal mortality in developed economies is around 12 per 100 000 live births (0.012%) and 239 per 100 000 live births (0.2%) in emerging economies, with large disparities both between and within countries [3]. Cardiovascular diseases also have the first place among extragenital diseases in the structure of the causes of perinatal morbidity and mortality [2, 21]. Arterial hypertension (AH) occupies a leading position among these cardiovascular diseases. AH promotes the development of long-term vascular and metabolic disorders [4]. There is a

decrease in placental blood flow in pregnant women with AH due to changes in the functioning of the cardiovascular system. Disturbances of the normal relationship between vasodilators and vasoconstrictors in pregnant women with AH are accompanied by dysregulation of vascular tone and leads to placental insufficiency [5]. One of the leading theories of placental insufficiency is vascular-endothelial dysfunction theory [6]. 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 [7].

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

angiogenic properties [8, 9, 10, 11]. The placental growth factor (PIGF) 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 [12, 13, 14, 15]. During the third trimester of pregnancy PIGF expression reaches a maximum of 28-30 weeks of gestation, gradually increasing from the first to the second trimester of pregnancy [16, 18]. Anti-angiogenic factors include placental soluble fms-like tyrosine kinase (sFlt-1) [17]. It counteracts the action of PIGF on specific receptors [19]. The imbalance between pro- and anti-angiogenic factors contributes to placental insufficiency [9, 11, 19].

Estradiol (E) is the main hormone of pregnancy. Reduced E, its constantly low concentration, or insufficient growth indicate a violation of the fetoplacental complex [22, 23]. Chorionic gonadotropin (CHG) appears in the blood of the mother on 8-9 days after fertilization of the egg. During the first trimester of pregnancy, CHG levels are rapidly increasing, doubling every 2-3 days, reaching its maximum at 8-10 weeks of gestation. After that, its content is somewhat reduced and remains constant during the second half of pregnancy [24, 25, 26, 27]. Progesterone (PG) improves the conditions for trophoblast migration in 1-2 gestational trimesters by stimulating the growth and remodeling of the coiled arteries of the uterus, increasing the expression of the vascular endothelial growth factor and its receptor [28].

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

**The objective:** to detect peculiarities of angiogenesis factors and hormonal profile in pregnant women with arterial hypertension 1 and 2 grade.

**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 88 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, who were included in the first – the main group (mean age was 27.7 ± 1.7 years). The second control group included 27 healthy pregnant women with physiological pregnancies (mean age – 27.9 ± 1.4). 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 in blood serum: chorionic gonadotropin (HCG), progesterone (PG), estradiol (E). Among the markers of angiogenesis in blood serum, the following were determined: 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 stages of research were carried out with the assurance of the rights and freedoms of patients provided for by the Declaration of Helsinki (Declaration of Helsinki 1964 - 2000) of the International Conference on Harmonization (ICH) and compliance with the standards of good clinical practice (GCP), the Convention of the Council of Europe on the protection of human rights and dignity in connection with the use of achievements of biology and medicine (from 04.04.1997).

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.

Table 1

**Levels of angiogenesis in groups of pregnant women**

Indexes	I group, n=61 Me (Q25; Q75)	control group, n=27 Me (Q25; Q75)	P
PIGF, pg/ml	9,1 (3,8; 19,2)	33,6 (26,8; 45,6)	< 0,001
sFlt-1, pg/ml	1700,9 (1315,6; 2005,6)	1419,7 (1060,3; 1673,5)	< 0,05
K	184,5 (59,5; 565,3)	34,7 (24,1; 53,7)	< 0,001

Table 2

Levels of pregnancy hormones in groups of pregnant women

Indexes	I group, n=61 Me (Q <sub>25</sub> ; Q <sub>75</sub> )	control group, n=27 Me (Q <sub>25</sub> ; Q <sub>75</sub> )	P
PG, ng/ml	33,8 (26,2; 43,8)	30,5 (27,1; 44,9)	> 0,05
E, pg/ml	2226,8 (1488,3; 3333,3)	2512,9 (1778,4; 3562,5)	> 0,05
CHG, ng/ml	534,6 (424,9; 611,3)	501,3 (456,9; 616,9)	> 0,05

Table 3

The relationship between PIGF and pregnancy hormones in groups of women

Indexes	I group, n=61 Me (Q <sub>25</sub> ; Q <sub>75</sub> )	control group, n=27 Me (Q <sub>25</sub> ; Q <sub>75</sub> )	P
CHG/PIGF	51,8 (22,6; 168,6)	14,8 (10,4; 17,8)	< 0,001
E/PIGF	309,7 (129,1; 724,6)	70,0 (49,2; 96,2)	< 0,001
PG/PIGF	4,8 (1,5; 9,2)	1,0 (0,6; 1,2)	< 0,001

Table 4

The results of the correlation analysis between angiogenesis and pregnancy hormones in group I

Indexes	PIGF	sFlt-1	PG	E	CHG
PIGF	-	-0,13	-0,29 *	-0,21	-0,19
sFlt-1		-	-0,06	0,05	0,07
PG			-	0,5 *	0,13
E				-	0,1
CHG					-

Note. \* – p<0.05.

Table 5

The results of the correlation analysis between angiogenesis and pregnancy hormones in the control group

Indexes	PIGF	sFlt-1	PG	E	CHG
PIGF	-	-0,09	0,04	0,16	0,43 *
sFlt-1		-	0,12	-0,13	0,13
PG			-	0,25	0,22
E				-	0,2
CHG					-

Note. \* – p<0.05.

## RESULTS AND THEIR DISCUSSION

We could say that assessing the average levels of angiogenic factors, found a statistically significant difference between the groups, p>0,05 (tab. 1).

It was found that the level of PIGF was significantly reduced in persons of group I 3.7 times: 9.1 (3.8; 19.2) pg / ml against 33.6 (26.8; 45.6) pg / ml in women of the II group, p<0,001. The rate of sFlt-1, in contrast, was higher in pregnant women with CAH: 1700.9 (1315.6; 2005.6) pg / ml against 1419.7 (1060.3; 1673.5) pg / ml, p<0, 05. Given the changes in the markers of angiogenesis, it was decided to calculate the ratio of these factors (soluble fms-like tyrosine kinase to placental growth factor) to each other. The ratio of sFlt-1 to PIGF was denoted by the coefficient K. Accordingly, K was significantly increased in persons of group I in 5.3 times: 184.5 (59.5; 565.3) units against 34.7 (24.1; 53.7) units, p<0.001.

Assessing hormone levels in pregnant women (progesterone, estradiol, human chorionic gonadotropin), no sta-

tistically significant difference was found between groups, p>0.05 (tab. 2).

The situation was somewhat different when comparing the ratios of PIGF and pregnancy hormones with each other (tab. 3).

Thus, the rate of CHG / PIGF was 3.5 times higher in women with CAH than the corresponding rate of pregnant women with a physiological course of pregnancy. The E / PIGF index exceeded 4.4 times, and the PG / PIGF- 4.8 times, respectively, p<0.001 for all indicators.

Correlation analysis between angiogenesis and pregnancy hormones in group I of women with CAH revealed that PIGF and CHG had a weak force feedback (R = -0.29), PG and E levels – a direct link of medium strength (R = +0.50). Statistically significant correlations were not determined between other data (tab. 4).

The corresponding analysis in women of the control group showed that PIGF and CHG had a direct relationship of medium strength (R = + 0.43) (p<0.05).

Other indicators did not have reliable relationships (tab. 5).

Thus, it was found that in the first trimester of pregnancy (11-12 weeks of gestation) in women with CAH is determined by a shift in the balance between pro- and antiangiogenic factors, manifested by statistically significant ( $p < 0.05$ ) increase in sFlt-1 levels (1700,9 pg/ml) and a decrease in PlGF levels in 3.7 times (9.1 pg/ml) and, accordingly, an increase in the levels of the coefficient K in 5.3 times (sFlt-1 / PlGF) (184.5).

The mean values of estradiol, progesterone and chorionic gonadotropin levels in pregnant women with CAH did not differ statistically significantly from those of the control group ( $p > 0.05$ ). However, according to the results of correlation analysis, the indicators of PlGF and PG have feedback in pregnant women with CAH ( $r = -0.29$ ;  $p < 0.05$ ).

When calculating the correlation of PlGF and hormones, it was found that in pregnant women with CAH there is their growth according to the control group,

namely the indicator CHG correlates with PlGF (51.8 units vs. 14.8 units) 3.5 times, E correlates with PlGF (309.7 units vs. 70.0 units) 4.4 times and PG correlates with PlGF (4.8 units vs. 1.0 units) 4.8 times,  $p < 0.001$  for all indicators. These changes indicate the presence of angiogenesis disorders in pregnant women with chronic hypertension, starting from the first trimester of gestation.

## CONCLUSIONS

1. Pregnant women with CAH in 1 trimester have disturbances in balance between pro-angiogenic and anti-angiogenic factors with prevalence of sFlt-1 and reducing of PlGF in serum.

2. Due to such disbalance in pregnant women with CAH of 1 and 2 grade changed cooperation between angiogenesis factors and hormones from direct to inverse.

3. It may lead to development of placental insufficiency in future. That's why treatment/prophylaxis of it should be administered to pregnant women with CAH in 1 trimester.

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Стаття надійшла до редакції 06.04.2022. – Дата першого рішення 12.04.2022. – Стаття подана до друку 17.05.2022