Factors of angiogenesis and placental hormones in pregnant women with arterial hypertension

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article;
E – critical revision of the article; F – final approval of the article

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

Aim. To detect peculiarities of angiogenesis factors and placental hormones in pregnant women with arterial hypertension I and II grades in comparison with results of healthy pregnant women.

Materials and methods. A one-time study of pregnant women was performed in pregnancy of 12–13 weeks in all groups. 88 pregnant women were inspected. The 1st basic group consisted of 28 pregnant women with AH of I grade; the 2nd group consisted of 33 pregnant women with AH of II grade; the comparison group included 27 women without AH. The following hormones were determined: HCG, 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. Statistical analysis was done by using Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Results. Pregnant women in 1st group were the youngest: the average age was 26.4 ± 0.8 years versus 33.8 ± 0.6 years in 2nd group and 32.0 ± 1.0 years in control group, $P < 0.001$. PGF levels were decreased in both 1st (17.5 ± 3.4 pg/ml) and 2nd groups (13.5 ± 2.5 pg/ml) in comparison with results in 3rd group (46.1 ± 7.0 pg/ml), $P < 0.001$. We didn't find statistical differences between results of women with AH of I and II degree, $P > 0.05$. Contrary to previous results, sFlt-1 levels were increased in both 1st and 2nd groups, $P < 0.05$: 1703.1 ± 99.2 pg/ml in 1st group and 1673.7 ± 93.5 pg/ml in 2nd group versus 1384.4 ± 77.1 pg/ml in control group, but they weren't different between basic groups, $P > 0.05$. As a result, sFlt-1/PGF ratio level was increased in both 1st (273.3 ± 54.6 units) and 2nd (415.8 ± 79.0 units) groups in comparison with control (46.6 ± 9.4 units), $P < 0.001$. We didn't set statistical differences in hormones levels among pregnant patients. PGF level was connected with E ($r = -0.54$, $P < 0.01$) and HCG ($r = -0.42$, $P < 0.05$) levels in pregnant women with AH of I degree. It was connected with HCG level in control group, but this correlation was contrary: $r = +0.63$, $P < 0.001$.

Conclusions. Pregnant women with AH in I trimester have disturbances in balance between pro-angiogenic and anti-angiogenic factors with prevalence of sFlt-1 and reducing of PGF in blood serum. Due to such disbalance in pregnant women with AH of I grade correlation between angiogenesis factors and hormones changed from direct to inverse.

Фактори ангіогенезу та плацентарні гормони у вагітних з артеріальною гіпертензією

О. В. Дейніченко, Ю. Я. Круть

Зміни факторів ангіогенезу та гормонів вагітності у жінок із гіпертензією (АГ) I та II ступенів вивчені недостатньо, а їхня взаємодія в таких пацієнток достеменно не встановлена.

Мета роботи – визначити особливості факторів ангіогенезу та плацентарних гормонів у вагітних жінок з АГ I та II ступенів порівняно з результатами здорових вагітних.

Матеріали та методи. Виконали одномоментне дослідження вагітних у термінах вагітності 12–13 тижнів у всіх групах. Обстежили 88 вагітних: у 1 основну групу ввійшли 28 вагітних з АГ I ступеня; 2 група включала 33 вагітних із АГ II ступеня; у групу порівняння ввійшли 27 вагітних жінок без АГ. Досліджували сироватку крові, визначали гормони: хоріонічний гонадотропін (ХГЛ), прогестерон (ПГ), естрадіол (Е). Серед показників ангіогенезу досліджували плацентарний фактор росту (PGF) як про-ангіогенний фактор, а також плацентарну розчинну тирозинкіназу (sFlt-1) як анти-ангіогенний фактор; обчислювали sFlt-1/PGF співвідношення. Статистичний аналіз виконали за допомогою програми Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результати. Вагітні 1 групи були наймолодшими – їхній середній вік становив $26,4 \pm 0,8$ року проти $33,8 \pm 0,6$ року в жінок 2 групи та $32,0 \pm 1,0$ року у вагітних контрольної групи, $p < 0,001$. Рівні PGF були зниженими в 1 ($17,5 \pm 3,4$ пг/мл) і 2 ($13,5 \pm 2,5$ пг/мл) групах порівняно з показниками 3 ($46,1 \pm 7,0$ пг/мл) групи, $p < 0,001$. Не встановили статистичну різницю між показниками жінок із АГ I та II ступенів, $p > 0,05$. На відміну від цих даних, рівні Flt-1 були підвищеними в 1 і 2 групах, $p < 0,05$: $1703,1 \pm 99,2$ пг/мл у 1 групі та $1673,7 \pm 93,5$ пг/мл у 2 групі проти $1384,4 \pm 77,1$ пг/мл у контрольній групі, але вони не відрізнялися в пацієнток основних груп, $p > 0,05$. Як результат, співвідношення sFlt-1/PGF було підвищеним в 1 ($273,3 \pm 54,6$ одиниці) і 2 ($415,8 \pm 79,0$ одиниці) групах порівняно з контролем ($46,6 \pm 9,4$ одиниці), $p < 0,001$. Не виявили статистично значущу різницю між групами вагітних за рівнями плацентарних гормонів. Рівні PGF були пов'язані з рівнями Е ($r = -0,54$, $p < 0,01$) та ХГЛ ($r = -0,42$, $p < 0,05$) у вагітних з АГ I ступеня. Рівень PGF також був пов'язаний із рівнем ХГЛ у контрольній групі, але ця кореляція була іншого напряму – $r = +0,63$, $p < 0,001$.

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Висновки. У вагітних з АГ у I триместрі визначили порушення балансу між про-ангіогенними та анти-ангіогенними факторами з переважанням sFlt-1 і зниженням PGF у сироватці крові. У зв'язку з таким дисбалансом у вагітних із АГ I ступеня змінюється на протилежну кореляція між факторами ангіогенезу та гормонами.

Факторы ангиогенеза и плацентарные гормоны у беременных с артериальной гипертензией

Е. В. Дейниченко, Ю. Я. Круть

Изменения факторов ангиогенеза и гормонов беременности у женщин с артериальной гипертензией (АГ) I и II степеней изучены недостаточно, а их взаимодействие у таких пациенток полностью не определено.

Цель работы – установить особенности факторов ангиогенеза и плацентарных гормонов у беременных с АГ I и II степеней в сравнении с результатами здоровых беременных.

Материалы и методы. Провели одномоментное исследование беременных в сроках беременности 12–13 недель во всех группах. Обследовали 88 беременных: 1 основная группа состояла из 28 беременных с АГ I степени; 2 группа включала 33 беременных с АГ II степени; в группу сравнения вошли 27 беременных без АГ. Исследовали сыворотку крови, определяли гормоны: хорионический гонадотропин (ХГЧ), прогестерон (ПГ), эстрадиол (E). Среди показателей ангиогенеза исследовали плацентарный фактор роста (PGF) как про-ангиогенный фактор, а также плацентарную растворимую тирозинкиназу (sFlt-1) как анти-ангиогенный фактор; вычисляли sFlt-1/PGF соотношение. Статистический анализ провели с помощью программы Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J).

Результаты. Беременные 1 группы были самыми молодыми – их средний возраст составил 26,4 ± 0,8 года против 33,8 ± 0,6 года женщин 2 группы и 32,0 ± 1,0 года у беременных контрольной группы, p < 0,001. Уровни PGF были снижены в 1 (17,5 ± 3,4 пг/мл) и 2 (13,5 ± 2,5 пг/мл) группах в сравнении с данными 3 (46,1 ± 7,0 пг/мл) группы, p < 0,001. Не установлена статистическая разница между результатами женщин с АГ I и II степеней, p > 0,05. В отличие от этих данных, уровни Flt-1 были повышенными в 1 и 2 группах, p < 0,05: 1703,1 ± 99,2 пг/мл в 1 группе и 1673,7 ± 93,5 пг/мл во 2 группе против 1384,4 ± 77,1 пг/мл в контрольной группе, но они не отличались у пациенток основных групп, p > 0,05. Как результат, соотношение sFlt-1/PGF было повышенным в 1 (273,3 ± 54,6 единицы) и 2 (415,8 ± 79,0 единицы) группах сравнительно с контролем (46,6 ± 9,4 единицы), p < 0,001. Не установлена статистически значимая разница между группами беременных по уровням плацентарных гормонов. Уровни PGF связанны с уровнями E (r = -0,54, p < 0,01) и ХГЧ (r = -0,42, p < 0,05) у беременных с АГ I степени. Уровень PGF также связан с уровнем ХГЧ в контрольной группе, хотя эта корреляция была обратной – r = +0,63, p < 0,001.

Выводы. У беременных с АГ в I триместре установлено нарушение баланса между про-ангиогенными и анти-ангиогенными факторами с преобладанием sFlt-1 и снижением PGF в сыворотке крови. В связи с таким дисбалансом у беременных с АГ I степени меняется на обратную корреляция между факторами ангиогенеза и гормонами.

Cardiovascular diseases have the first place among extragenital diseases in the structure of the causes of perinatal morbidity and mortality. Arterial hypertension (AH) occupies a leading position among these cardiovascular diseases. AH promotes the development of long-term vascular and metabolic disorders [1,2]. 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 [3,4]. 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 [5].

The activity of placental angiogenesis is controlled by a spectrum of growth factors with pro-angiogenic and anti-angiogenic properties. The placental growth factor (PGF) 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 PGF expression reaches a maximum of 28–30 weeks of gestation, gradually increasing from the first to the second trimester of pregnancy [6,7]. Anti-angiogenic factors include placental soluble fms-like tyrosine kinase (sFlt-1). It counteracts the action of PGF on specific receptors [8]. The imbalance between pro- and anti-angiogenic factors contributes to placental insufficiency [6].

Estradiol (E) is the main hormone of pregnancy. Reduced E, its constantly low concentration, or insufficient growth indicate a violation of the fetoplacental complex. Human chorionic gonadotropin (HCG) appears in the blood of the mother on 8–9 days after fertilization of the egg. During the first trimester of pregnancy, HCG levels are rapidly increasing, doubling every 2–3 days, reaching its maximum at 8th-10th weeks of gestation. After that, its content is somewhat reduced and remains constant during the second half of pregnancy [9]. Progesterone (PG) improves the conditions for trophoblast migration in 1st–2nd 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 [10].

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

Aim

To detect peculiarities of angiogenesis factors and placental hormones in pregnant women with arterial hypertension I and II grades in comparison with the results of healthy pregnant women.

Materials and methods

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

A one-time study of pregnant women was performed in pregnancy of 12–13 weeks in all groups. 88 pregnant women were inspected. The 1st basic group consisted of 28 pregnant women with AH of I grade; the 2nd group consisted of 33 pregnant women with AH of II grade; the comparison group included 27 women without AH. Anamnesis, general clinical examination, blood pressure measurement, standard obstetric and gynecological examination according to clinical protocols were done in all cases. AH was diagnosed according to the existing clinical protocols.

The following hormones were determined: HCG, 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 Zaporizhzhia State Medical University. For this purpose, the microplate reader Sirio-S (Seac, Italy) was used. Blood serum was examined. 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: HCG, PG, E (Monobind Inc, USA); PGF and sFlt-1 (R&D systems, Inc, USA&tCanada).

Statistical analysis was done by using Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J). Normality of data 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 Spearmen method; statistically significant results were considered with a coefficient of more than 0.3 and with a level of P < 0.05.

The Bioethical committee of Zaporizhzhia State Medical University decided that scientific work corresponds to all the requirements of moral and ethical standards (Protocol number 2 from 03/22/2017).

Results

We could say, that pregnant women in 1st group were the youngest: the average age was 26.4 ± 0.8 years versus 33.8 ± 0.6 years in 2nd group and 32.0 ± 1.0 years in control group, P < 0.001. It may be explained, that progression of AH needs some time from beginning. PGF levels were decreased in both 1st (17.5 ± 3.4 pg/ml) and 2nd groups (13.5 ± 2.5 pg/ml) in comparison with results in control group (46.1 ± 7.0 pg/ml), P < 0.001. We didn't find statistical differences between results of women with AH of I and II degree, P > 0.05. Contrary to previous results, sFlt-1 levels were increased in both 1st and 2nd groups, P < 0.05: 1703.1 ± 99.2 pg/ml in 1st group and 1673.7 ± 93.5 pg/ml in 2nd group versus 1384.4 ± 77.1 pg/ml in control group, but they weren't different between basic groups, P > 0.05. As a result, sFlt-1/PGF ratio level was increased in both 1st (273.3 ± 54.6 units) and 2nd (415.8 ± 79.0 units) groups in comparison with control (46.6 ± 9.4 units), P < 0.001. But it was the highest in pregnant women with AH of II grade (*Fig. 1*).
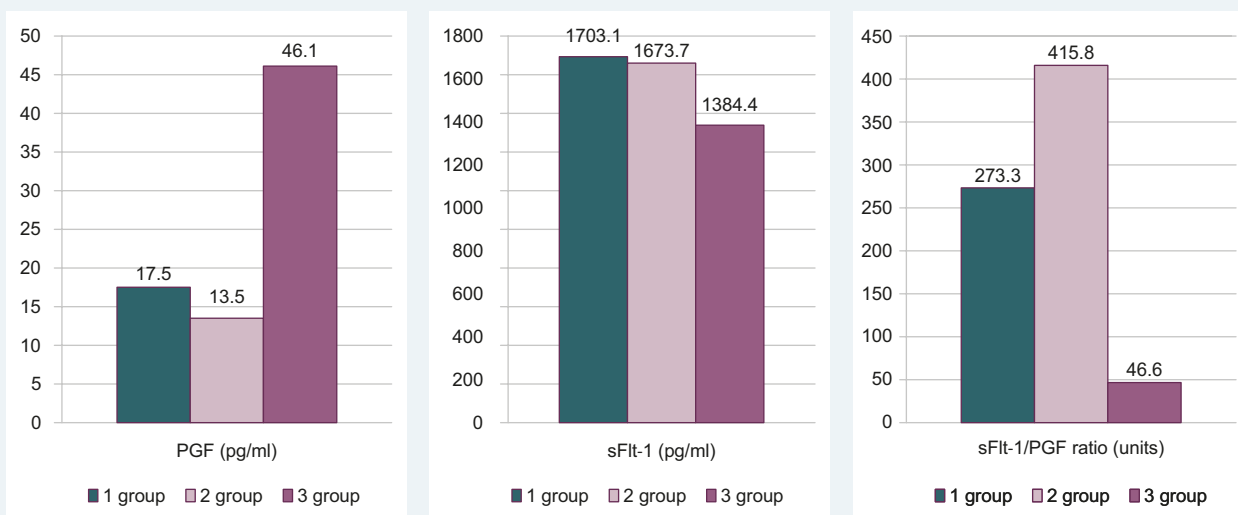

Fig. 1. Angiogenesis factors and sFlt-1/PGF ratio in groups of women.

Table 1. Hormones levels in groups of women, M ± m

Indicators, units	1st group, n = 28	2nd group, n = 33	Control group, n = 27	P
PG, ng/ml	32.0 ± 2.4	38.6 ± 3.0	36.1 ± 2.7	>0.05
E, pg/ml	2449.1 ± 228.7	2522.5 ± 230.4	2836.2 ± 268.6	>0.05
HCG, ng/ml	516.1 ± 21.9	513.3 ± 22.6	521.3 ± 23.0	>0.05

We didn't dedicate statistical differences among pregnant patients in hormones levels, P > 0.05 for all indicators. There were only a little reducing in PG level in women with AH of I degree: 1.2 times as compared to 2nd group and 1.1 times as compared to control group (*Table 1*).

PGF level was connected with E (r = -0.54, P < 0.01) and HCG (r = -0.42, P < 0.05) levels in pregnant women with AH of I degree. It was connected with HCG level in control group, but this correlation was contrary: r = +0.63, P < 0.001. We couldn't detect any correlations between indicators in patients from 2nd group, P > 0.05.

Discussion

We detected reducing of PGF and growing of sFlt-1 (as sFlt-1/PGF ratio) in pregnant women with AH of both I and II grades. The similar results had group of authors [11,12]. But these authors examined patients in II trimester of pregnancy. PGF sFlt-1 levels were also detected [13], they included them to prognosis of preeclampsia and showed their levels in 1st trimester. The highest sFlt-1/PGF ratio was in pregnant women with AH of II grade, that may indicate progression of pathological changes after several years of living with arterial hypertension. But we didn't find any statistical differences in hormones levels between groups of patients. Another results were received by groups of scientists [9,14,15]. They found decrease of E levels in pregnant women. Contrary to literature results we examined both angiogenesis factors and hormones. We defined inverse correlations between PGF levels and two hormones levels (E and HCG) in women with AH of I grade versus to direct correlation between this pro-angiogenesis factor and HCG in control group. It may indicate disturbances in cooperation of such indicators in case of AH beginning. We suppose, such changes may lead to development of placental insufficiency in future. That's why treatment/prophylaxis of it should be administered to pregnant women with AH of I grade in I trimester.

Conclusions

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

2. Due to such disbalance in pregnant women with AH of I grade correlation between angiogenesis factors and hormones changed from direct to inverse.

Future researches plans. We plan to find features of angiogenesis factors and hormones changes in patients with arterial hypertension with fetal growth retardation and to detect early indicators of such complication of placental insufficiency.

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