ORIGINAL ARTICLE

THE ROLE OF SECRETING FUNCTION OF DECIDUA IN THE DEVELOPMENT OF COMPLICATIONS OF GESTATION PROCESS IN PREGNANT WOMEN WITH A PAST HISTORY OF CHRONIC ENDOMETRITIS

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ABSTRACT

The aim: To determine the serum FAMG in the I and II trimester of pregnancy in women with a past history of chronic endometritis, and to clarify its impact on the development of pathology of pregnancy.

Materials and methods: The level of FAMG was determined at 6-8 and 16-18 weeks of gestation in 135 pregnant women with a past history of chronic endometritis, who received treatment of chronic endometritis at the stage of pregravid preparation and 168 women who became pregnant without its prior treatment. The dependence of the development of pre-eclampsia on the level of FAMG at the early stages of pregnancy has been evaluated.

Results: At 6-8 weeks of pregnancy, the level of FAMG in women with a past history of chronic endometritis was 20.6% lower (122.4 ± 7.6 ng/ml) compared to the control group. In FAMG of 90.3 ± 4.3 ng/ml at 6-8 weeks of gestation, spontaneous abortion occurred in 100% of cases within the next 2 weeks. FAMG lower than 122,1 ± 3,0 ng/ml can be the predisposing factor for the development of pre-eclampsia.

Conclusions: Reduced FAMG in the beginning of pregnancy in women with untreated chronic endometritis in the past history increases the incidence of miscarriages at the early stages by 2.6 times, and by 1.8 times the probability of preeclampsia development. Treatment of chronic endometritis at the stage of pregravid preparation promotes the increase of FAMG by 24,6% compared to untreated women that reduces the probability of complications during the subsequent course of pregnancy.

KEY WORDS: chronic endometritis, pre-eclampsia, fertility α2-microglobulin, habitual noncarrying of pregnancy

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INTRODUCTION

Prevention of preeclampsia is crucial in management of pregnancy, since this pathology causes perinatal and maternal morbidity and mortality not only in Ukraine but also worldwide [1]. This issue is especially important in the context of the ineffectiveness of any treatment for this pathology, since its occurrence is due to pregnancy itself and is formed much earlier than the onset of the first symptoms [2]. Pre-eclampsia (PE), like most placental pathologies, is associated with the disturbances in the formation of utero-placental blood flow at the stage of trophoblast invasion into the spiral arteries of the uterus [2,3]. Adequate endovascular migration of trophoblast leads to the destruction of the smooth muscles of the spiral arteries, leading to substitution with the fibrinoid masses, and, consequently, the minute vessels of the uterus transform into wide channels with low resistance and relative tolerance to the action of vasopressor factors [2,3]. This is how the massive and stable utero-placental blood flow is formed. The study of placental bed and uterine wall biopsy after hysterectomy showed that in the course of physiological pregnancy, up to 95% of the spiral arteries of the uterus, participating in the formation of the placenta, are subject to trophoblastic changes [3]. At the same time, with the development of pre-eclampsia, only 40% of arteries are transformed [3]. Unchanged vessels retain the endothelial layer, which is the basis for the development of endothelial dysfunction, vasoconstrictions [2] and impaired blood flow in the uterine and spiral arteries in pre-eclampsia [4].

Thus, the development of pre-eclampsia occurs in the beginning of pregnancy and in this process the interaction of three components is crucial: fetal (trophoblast), maternal (endometrium, transformed into the uterine decidua, spiral vessels), and immunological (factors that determine the tolerance of the mother to the "fetal transplant" and regulate the process of both interstitial and endovascular invasion of the trophoblast) [2,3]. In the regulation of the trophoblast invasion the maternal aspect is ensured by the ability of the decidual membrane to synthesize fertility α2-microglobulin (FAMG) [5]. FAMG (glycodelin-A) is a glycoprotein secreted by the glands of the endometrium and the decidual membrane [5,6]. It is a powerful stimulator for the synthesis of monocytes and macrophages of the Interleukin-6 [5], which plays an important role in the trophoblast invasion, since it increases the activity of matrix metalloproteinases, induces chemotaxis and cellular migration [5,6]. On the other hand, the inadequate development of FAMG (for example, concomitant with

chronic intrauterine infection in chronic endometritis (CE) in the past history before pregnancy [7,8]) may be one of the mechanisms that limit the invasive capacity of trophoblast and lead to pathology of pregnancy associated with the formation of the placenta at the early stages (and prior pre-eclampsia).

THE AIM

The paper was aimed at determining the serum FAMG in the I and II trimester of pregnancy in women with a past history of chronic endometritis and to clarify its impact on the development of pathology of pregnancy.

MATERIALS AND METHODS

A comprehensive clinical-laboratory and instrumental study of women, who planned pregnancy, became pregnant and gave birth to children in medical facilities of Poltava city and Poltava region from 2010 to 2018 was carried out. The administration of the medical facilities and the subjects were fully informed about the purpose of our research and signed the written consent form. All studies performed during the course of work were approved by the Ethics and Biomedical Ethics Commission of the Ukrainian Medical Stomatological Academy and were conducted in accordance with the Rules of Humane Treatment of Patients in compliance with the requirements of the Tokyo Declaration of the World Medical Association, the International Recommendations of the Helsinki Declaration on Human Rights, the Convection of the Council of Europe human rights and biomedicine, Laws of Ukraine, Orders of the Ministry of Health of Ukraine and the requirements of the Ethical Code of Ukrainian Doctor.

20 healthy pregnant women with unremarkable medical history (control group) and 303 pregnant women who had histologically confirmed signs of CE diagnosed before pregnancy (main group) were examined. Among women of the main group 135 women received treatment of CE at the stage of pregravid preparation according to the developed regiment (Group I). The latter included antibacterial, anti-inflammatory, antiviral and metabolic drugs, as well as progesterone (in hypertrophic forms of CE) or femostone 2/10 (in case of atrophic CE) during 3 months. The choice of antibacterial drug was made taking into account the pathogen, and in the event that it was not detected, 500 mg azithromycin was used daily from the beginning of menstruation for 3 days with subsequent repeated course during the next menstruation at the same dosage. Other 168 pregnant women of the main group refused from the treatment of CE during the pregravid preparation (Group II), which was documented in writing.

Since chronic endometriosis, diagnosed before pregnancy, can develop pre-eclampsia, we monitored the course of pregnancy to detect presence or absence of signs of this complication. In addition, at 6-8 and 16-18 weeks of pregnancy, a blood test was made to determine the serum FAMG. Upon gestation, patients in both groups were retrospectively divided into subgroups depending on the presence and severity of PE: "no pre-eclampsia" subgroup, "moderate pre-eclampsia" subgroup and "severe pre-eclampsia" subgroup. In order to find out whether the change of FAMG values in the beginning of pregnancy is associated with the manifestations of PE in later periods of the gestational process, the serum FAMG at 6-8 and 16-18 weeks of pregnancy was retrospectively evaluated in women of these subgroups, using the "Fertitest-M" test system. The method is based on the principle of enzyme-linked immunosorbent assay, which includes the immunological response of the antigen-antibody on the sandwich principle and the enzymatic reaction, which leads to the development of color changes of the solution of chromogen depending on the concentration of antigen (sandwich ELISA).

RESULTS

At 6-8 weeks of pregnancy, serum FAMG in women, who did not receive pregravid treatment of CE was 122.4 ± 7.6 ng/ml, which was significantly lower the control values for this period (154.0 ± 7.1 ng/ml, ($p<0.05$)). In women who became pregnant after treatment of CE, the level of FAMG (152.5 ± 7.3 ng/ml) exceeds the value in the group of untreated women before pregnancy by 24.6%, approximating to the reference values ($p<0,05$)).

With the development of pregnancy, the amount of blood FAMG decreases, accounting for 96.4 ± 4.2 ng/ml at 16-18 weeks of pregnancy in women of the control group, which was 37.5% lower the values recorded at 6-8 weeks of pregnancy. At this term no significant difference compared to FAMG values in the control group was noted in women of Group I and Group II (93.2 ± 7.1 ng/ml and 85.0 ± 9.6 ng/ml, respectively, $p> 0.05$).

Noteworthy, 4 women of Group I (2.96%) and 23 women of Group II (13.7%) had miscarriage before 8 weeks of pregnancy. The serum FAMG in women with spontaneous abortion before 8 weeks of gestation was an average of 90.3 ± 6.9 ng/ml, which was extremely low for this term of pregnancy (58.6% lower the control values of 154.0 ± 7.1 ng/ml ($p <0.05$)).

At 8-12 weeks of pregnancy, 8 women of Group I (5.9%) and 16 women of Group II (9.5%) experienced spontaneous abortion. Between 12 and 22 weeks of pregnancy, 2 more women of Group I (1.48%) and 2 women in Group II (1.2%) had pregnancy loss. We have calculated the level of FAMG in women with pregnancy loss before 16-18 weeks of gestation, recorded at 6-8 weeks' gestation period. It was 28% lower than the control values and was 111.4 ± 6.6 ng/ml ($p <0.05$).

After 22 weeks of pregnancy, 1 woman (0.74%) of Group I and 2 women (1.2%) in Group II experienced premature labor. The examined women of Group I (n=2 (1.5%)) and Group II (n=15 (8.9%)), who required premature delivery due to obstetric pathology, gave birth to preterm babies. The causes of premature delivery were fetal distress (in this case, cesarean section was performed for one woman

(0.74%) of Group I and 6 women (3.6%) of Group II) before 36 weeks of pregnancy), intrauterine growth restriction associated with placental dysfunction and blood flow disorder in the utero-placental complex (3 women (1.78%) in Group II) and severe pre-eclampsia. Severe PE was the cause for premature delivery of 6 women (3.4%) in Group II and 1 woman (0.74%) in Group I.

Generally, PE complicated the course of pregnancy in 37 out of 116 women in Group II, who preserved their pregnancy to the third trimester of pregnancy (32.1%). In the group of women treated before pregnancy, this index was 17% (20 women out of 119 patients in Group I who preserved pregnancy to the third trimester of pregnancy).

Notably, moderate manifestations of PE were noted in women of Group I in 85% of cases (17 women), and severe PE was diagnosed only in 15% (3 women). Among women of Group II, severe PE occurred in 27% of cases (10 out of 37 women), and moderate manifestations of PE were noted in 73%. The average term when PE arose was 32.3 ± 0.4 weeks of pregnancy in Group I and 29.4 ± 0.6 weeks of pregnancy in Group II. Premature delivery, as mentioned above, required 1 woman from Group I and 6 women from Group II, accounting for 5% and 16.2%, respectively, for all PE women.

In women of both groups, whose pregnancy was complicated with moderate and severe PE, we calculated the serum FAMG values recorded at 6-8 weeks and 16-18 weeks of gestation. It has been found that FAMG value was 156.8 ± 7.0 ng/ml in women of Group I without developed PE at 6-8 weeks of pregnancy (almost no difference from the control values; p>0,05); in women who developed moderate PE the FAMG value was 131.9±3.9 ng/ml, which was 15% lower the control values and significantly different from them and from values in the subgroup without preeclampsia (p <0.05). In women of Group I, who developed severe pre-eclampsia, the beginning of pregnancy was accompanied by lower serum FAMG: 126.3 ± 1.5 ng/ml, which was 18% lower the values of the control group (p<0.05) and 19,5% lower the values of pregnant women without pre-eclampsia (p <0,05) and 4.3% lower the values of pregnant women with moderate pre-eclampsia (p> 0,05).

At 16-18 weeks of pregnancy, women of Group I who did not develop PE, FAMG was 95.8 ± 3.6 ng/ml, which was almost similar to reference values for this period (p> 0.05). In pregnant women, who developed moderate and severe PE, FAMG was 80.3 ± 4.8 ng/ml and 77.8 ± 1.5 ng/ml, respectively, that was 16,8% and 19,4%, respectively, less than the control values and differ significantly from them and from the values of the subgroup without pre-eclampsia (p<0,05).

The content of blood plasma FAMG in women, who did not receive treatment of CE during the pregravid preparation (Group II), had the same pattern. However, the reduction of FAMG in relation to the required values for corresponding term of pregnancy was even more pronounced in them. At 6-8 weeks of pregnancy the FAMG value in the subgroup of those women who developed moderate and severe PE was 20.8% (122.1 ± 3.2 ng/ml (p <0.05)) and 26,6% (113,1 ± 3,0 ng/ml; (p <0,05)), respectively that was lower than the control values. At 16-18 weeks of pregnancy, the decrease in FAMG relative to the control values (96.4 ± 4.2 ng/ml) was 24.9% in the subgroup of women with subsequent development of moderate PE (72.4 ± 2.5 ng/ml; p<0.05) and 31.3% in the subgroup of women with severe PE (66.2 ± 2.7 ng/ml; p<0.05).

DISCUSSION

The study demonstrated that the presence of CE in the past history impacted significantly the progress of the gestational process in women who became pregnant with such complication. This is especially true for the habitual noncarrying of pregnancy. We have stated that pregnancy loss in women with a past history of CE (without pregravid preparation) was approximately 34.5%, with the majority of them occurring at early stages of pregnancy, up to 8 weeks of gestation (the share of all miscarriages was 56.1%).

We consider this to be related to endometrial changes in chronic infections, which are accompanied by a decrease in the secretory capacity of its glands to the synthesis of FAMG and limit its implantation potential (invasive trophoblast ability decreases, implantation is impaired, which creates preconditions for abortion [3,6]). It has been proved by the works of numerous investigators who believe that the reduction of FAMG in CE is one of the prerequisites for the development of infertility in this pathology [9,10]. The findings of our research show that even at the onset of pregnancy with untreated CE, the level of FAMG is significantly lower (by 20.6%) than the control values and is associated with a higher incidence of abortion. Thus, FAMG values in women who lost their pregnancy during the I and II trimesters at 6-8 weeks of pregnancy was 35.4% lower, and those patients whose values did not exceed 90.3 ± 4.3 ng/ml within the next two weeks lost pregnancies in 100% of cases.

On the contrary, in women who received treatment of CE during pregravid preparation with the use of antibacterial and hormonal medications the level of FAMG at 6-8 weeks of pregnancy was by 24.6% higher than the FAMG level in untreated women, approximating to the control values for this period. Admittedly, the total share of miscarriages is also lower not only before 8 weeks of pregnancy (the percentage of reproductive losses in women who received treatment before pregnancy at this term is by 4.6 times lower than in women with untreated CE in the past history), but also between 8 and 12 weeks of pregnancy. Thus, in women who did not receive pregravid treatment of CE, spontaneous abortions at 8 to 12 weeks of pregnancy occurred in 9.5% of cases compared to only 5.9% in treated women. We hypothesize that reduction in the percentage of pregnancy loss by 1.6 times in this period in treated women is likely to be explained by more successful luteoplacental transition, ensured by the maintenance of the luteal phase of the menstrual cycle during pregravid preparation.

In addition to a significant share of spontaneous abortion, we have established a high rate of premature delivery, which in women with CE was mostly due to intrauterine growth restriction and fetal distress, as well as pre-eclampsia. The probable cause for these complications, including pre-eclampsia, is the impaired gestational transformation of the spiral arteries during the I and II wave of trophoblast cell invasion, which results in the disorder of normal blood flow formation in the utero-placental complex [2,4]. The deficiency of FAMG in women with CE in the past history [8] plays an important role in these processes due to reduced invasive capacity of the trophoblast [5]. This is confirmed by the findings of our study, indicating that the low level of FAMG in the beginning of pregnancy in women with CE in the past history is associated with a high incidence of subsequent pre-eclampsia development and its more severe course. Thus, the incidence of pre-eclampsia in women with CE in the past history was 32.1%, and in one third of cases it occurred in severe form and had an early manifestation (29.4 ± 0.6 weeks of pregnancy). In fact, the level of FAMG at 6-8 weeks of pregnancy in women whose pregnancy was subsequently complicated by the development of pre-eclampsia was on the average by 17% lower as compared to patients whose pregnancy was developing without pre-eclampsia. In women with severe manifestations of pre-eclampsia, serum FAMG at 6-8 weeks of pregnancy did not exceed the values of 113.1 ± 3.0 ng/ml.

Moreover, treatment of CE at the stage of pregravid preparation promote prevention of pre-eclampsia, since, the findings showed, that the incidence of pre-eclampsia and the probability of its severe manifestations in women after treatment is reduced by 1.8 times. At 6-8 and 16-18 weeks of pregnancy, women who received treatment had higher levels of FAMG (15.9% and 9.6%, respectively), which is likely to explain the protective effect of such treatment on the course of pregnancy and its ability to prevent the development of preeclampsia.

CONCLUSIONS

1. Untreated chronic endometritis, which occurred before gestation, increases the probability of miscarriage by 2.6 times at the early stages, as well as by 1.8 times the probability of preeclampsia development.
2. Reduced level of FAMG in the beginning of pregnancy is likely to be a prerequisite for the formation of complications of gestational process:
   - serum FAMG in women who became pregnant with CE in the past history and whose pregnancy was terminated before 8 weeks of gestation was 58.7% lower than the control values;
   - in women with untreated CE in the past history, who subsequently developed pre-eclampsia, the level of FAMG was by 23.0% lower than in the control group at 6-8 weeks of gestation.
3. Critical level of FAMG up to 90.3 ± 4.3 ng/ml at 6-8 weeks of pregnancy caused miscarriage in 100% of cases within the next 2 weeks.
4. The level of FAMG lower than 122,1 ± 3,0 ng/ml is considered the predisposing factor for the development of preeclampsia during the course of pregnancy.
5. Treatment of CE at the stage of pregravid preparation promotes the increase of the serum FAMG by 24,6%, by 4,6 times reduces the probability of spontaneous abortion at early stages, as well as by 1,8 times prevents the development of pre-eclampsia, especially its severe forms.

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