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CHANGES IN CYTOKINE BALANCE IN PREGNANT WOMEN WITH CHRONIC ENDOMETRITIS IN THE PAST MEDICAL HISTORY AND THEIR ROLE IN THE DEVELOPMENT OF PREECLAMPSIA

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Summary

Few data regarding the levels of TNF-α, INF-γ and IL-10 in the cervical mucus of pregnant women with the past medical history of chronic endometritis have been found. The abovementioned cytokines have the impact on the course of pregnancy as well as the processes of trophoblast invasion into the spiral arteries of the uterus. Deviations in their levels at the early stages of pregnancy may be associated with the development of preeclampsia at later stages.

Purpose:*to assess the levels of TNF, INF-γ and cytokine IL-10 in the cervical mucus of pregnant women with a past medical history of chronic endometritis. Additionally, the study aims to determine their role in the development of preeclampsia and evaluate the effectiveness of comprehensive preconception treatment in preventing cytokine imbalance and the occurrence of gestational complications.*

Method and Materials. *135 pregnant women with the past medical history of chronic endometritis have been supervised during their pregnancy and received preconception treatment (Group I), as well as 168 women, whose pregnancy occurred in the presence of untreated chronic endometritis (Group II). The control group (CG) involved 20 healthy women. Preconception treatment included the administration of azithromycin, hormonal therapy with Femoston-Comb 2/10, and L-arginine aspartate in combination with folate prophylaxis.*

During the study, the principles of patient-centered care were followed in accordance with the requirements of the Tokyo Declaration of the World Medical Association, the International Recommendations of the Helsinki Declaration on Human Rights, the Convention on Human Rights and Biomedicine of the Council of Europe, the Laws of Ukraine, the Orders of the Ministry of Health of Ukraine and the requirements of the Ethical Code of the Ukrainian physician.

The cytokine (TNF-α, INFγ, IL-10) analysis in the cervical mucus was performed at 5-, 17-18 and 32 weeks of pregnancy, using the enzyme-linked immunosorbent assay method with corresponding standard commercial reagent kits from the «Vector BEST» company. The obtained data were processed using mathematical statistical methods, calculating the mean sample values (M), variance (σ) and standard errors of the means (m). Student's t-test was used for assessment and the likelihood ratio was calculated using the «STATISTICA» software (StatSoft Inc., USA).

The paper is an excerpt from the initiative scientific research project of the Department of Obstetrics and Gynecology No. 2 at Poltava State Medical University, entitled «Optimization of approaches to the management of pregnancy in women at high risk of obstetric and perinatal pathology» (State registration number 0122U201228, duration:10.2022-09.2027).

Results. *In pregnant women with a past medical history of chronic endometritis an increase in the levels of INF-γ in cervical mucus by 2.1 times at 5-6 weeks ($p<0.001$), by 2.4 times at 17-18 weeks ($p<0.001$) and by 1.7 times at 32 weeks of pregnancy ($p<0.001$) compared to corresponding levels of this cytokine in healthy pregnant women, has been detected. Similarly, TNF-α was by 4.3 times greater at 5-6 weeks of pregnancy compared to the values in the control group ($p<0.001$), by 3.3 times greater at 17-18 weeks of pregnancy ($p<0.001$) and by 4.4 times at 32 weeks of pregnancy ($p<0.001$). All pregnant women with a past medical history of chronic endometritis who had levels of INF-γ in the cervical mucus greater than 66.4 pg/ml and/or levels of TNF-α greater than 90.9 pg/ml at 5-6 weeks of pregnancy subsequently manifested preeclampsia (OR 2.01; 95 % CI [1.1-7.12]; $p<0.05$ and OR 1.8; 95 % CI [1.2-6.29]; $p<0.05$ respectively). The level of IL-10 in their cervical mucus was by 4 times higher than the control values at 5-6 weeks of pregnancy ($p<0.0001$); by 3.1 times higher at 17-18 weeks of pregnancy ($p<0.0001$) and by 3 times higher at 32 weeks of pregnancy ($p<0.0001$). This compensates for the increase in pro-inflammatory cytokines, allowing the TNF-α/IL-10 ratio to remain at a level characteristic of healthy women throughout pregnancy. In treated women, the concentration of INF-γ is by 1.8 times lower than in untreated patients at 5-6 weeks of pregnancy ($p<0.0001$), by 2.1 times at 17-18 weeks of pregnancy ($p<0.0001$), and by 1.4 times at 32 weeks of pregnancy ($p<0.0001$). Similarly, TNF-α in cervical mucus was found to be lower by 3.6 times ($p<0.01$), 2.6 times ($p<0.0001$), and 4 times ($p<0.001$) respectively, in the specified terms. This helps to avoid excessive production of the anti-inflammatory cytokine IL-10.*

Conclusions. *In women who got pregnant with untreated chronic endometritis, an increased production of cytokines INF-γ and TNF-α at the early stages of pregnancy has been established. Comprehensive pregravidar treatment of chronic endometritis allows for the normalization of levels of anti-inflammatory cytokines INF-γ and TNF-α at the beginning of gestation, which creates conditions for preventing the development of preeclampsia. This leads to a 1.9 times reduction in the frequency of this complication (OR 2.3; 95 % CI [1.25-4.31]; $p<0.05$), a 1.8 times decrease in the frequency of severe forms of preeclampsia (OR 4.64; 95 % CI [1.23-17.48]; $p<0.05$) and a delay in the average onset of its manifestations by 4.9 weeks ($p<0.0001$).*

Key words: *Preeclampsia; Chronic Endometritis; INF-γ; TNF-α; Trophoblast Invasion into the Spiral Arteries of the Uterus.*

Introduction

The onset of pregnancy in women diagnosed with chronic endometritis (CE) can be associated with a high risk (from 33 % to 87 % of cases) of pregnancy loss [1-3]. The development of CE is associated with a number of pathological processes that significantly affect the functional state of the uterine mucosa, thereby creating unfavorable conditions for the onset of pregnancy [4,

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5]. These are primarily related to destructive changes in endometrial cells that occur during prolonged inflammation [6], impaired microcirculation in the basin of the uterine spiral arteries [4], inadequate transformation of the uterine mucosa during the menstrual cycle [4-7], as well as a decrease in the synthesis of α2-microglobulin of fertility (also known as glycodelin-A) [7, 8].

In our previous studies, a decrease in the level of fertility α2-microglobulin (glycodelin-A) was demonstrated in women with CE both in the preconception stage and during the first weeks of pregnancy [2, 7]. Adequate synthesis levels create favorable conditions for implantation and embryonic development [8, 9], as well as ensure adequate progression of trophoblast invasion into the uterine spiral arteries, which is a necessary step in the formation of adequate feto-maternal blood flow [10, 11]. The processes of trophoblast invasion into the spiral arteries of the uterus are crucial for the entire process of pregnancy, and their disruption leads to the development of serious obstetric pathologies (such as pregnancy loss, pre-eclampsia, intrauterine growth restriction, placental abruption) [11-14]. The influence of glycodelin-A on the invasive properties of trophoblasts is related to its ability to alter the intensity of cytokine synthesis: high concentrations promote increased production of IL-6, while reducing its level induces macrophages to increased production of INF-γ and TNF-α [15-17]. The latter, in addition to their ability to potentiate aggressive immune responses, have a significant limiting effect on the processes of spiral vascular transformation [17, 18]. TNF-α from decidual macrophages promotes the transformation of invasive trophoblasts into non-invasive ones, inhibits the migration of trophoblast cells, reduces their viability, thereby decreasing their resistance to the lytic effects of NK cells [18, 19]. INF-γ stimulates NK cells and cytotoxic T lymphocytes, leading to the formation of lymphokine-activated killer cells capable of damaging trophoblasts, and also inhibits the production of a number of trophoblast growth factors [17-19]. Elevated levels of IL-10, as the major anti-inflammatory cytokine, protect the fertilized egg from maternal antigenic immune aggression and are essential for successful pregnancy [20-22].

We did not find any studies on the levels of TNF-α, INF-γ and IL-10 in women who became pregnant with CE. The role of variations in the levels of these cytokines in the early stages of pregnancy in the development of pre-eclampsia in later stages has not been studied.

Aim: to assess the levels of pro-inflammatory cytokines (TNF, INF-γ) and anti-inflammatory cytokine (IL-10) in the cervical canal mucus of pregnant women with a past medical history of chronic endometritis. Additionally, the study aims to determine their role in the development of preeclampsia and evaluate the effectiveness of comprehensive preconception treatment in preventing cytokine imbalance and the occurrence of gestational complications.

Materials and Methods. 135 pregnant women with a history of CE were followed during pregnancy and treated for CE in the pre-pregnancy period (group I), and 168 women whose pregnancy occurred in the presence of untreated CE (group II). The control group (CG) included 20 healthy women who had not been diagnosed with CE prior to pregnancy.

The proposed comprehensive preconception treatment for CE was aimed at improving the chances of pregnancy. It included administration of azithromycin to eliminate intrauterine infection as a cause of inflammatory response in the endometrium and a source of stimulation for excessive production of pro-inflammatory cytokines in CE [23]; Hormonal therapy with Femoston-Comb 2/10 for at least 3 months prior to pregnancy to synchronize phase changes in the uterine mucosa and restore the associated synthesis of glycodelin-A by the endometrial glands; L-arginine aspartate at a dose of 6 g per day for 2 months to restore normal endometrial blood supply [24]. In addition, folate prophylaxis was administered at a dose of 400 mcg/day. At the onset of pregnancy, patients were prescribed drug support with dydrogesterone at a dose of 20 mg/day from the time of conception confirmation until 17-18 weeks of pregnancy. L-arginine aspartate was also prescribed at a dose of 6 g per day in two 28-day courses during the formation of the first (from 5-6 to 8-9 weeks of pregnancy) and second (from 12-13 to 16-17 weeks of pregnancy) waves of trophoblast invasion into the spiral arteries of the uterus [12]. In accordance with current guidelines, pre-eclampsia prophylaxis was performed by administering acetylsalicylic acid at a dose of 100 mg/day from the 12th to the 36th week of pregnancy and calcium supplements at a dose of 1.5 g of elemental calcium per day from the 16th week of pregnancy until delivery. The dose of folic acid has been increased to 800 mcg/day during aspirin prophylaxis [25].

During the study, the principles of patient-centered care were followed in accordance with the requirements of the Tokyo Declaration of the World Medical Association, the international recommendations of the Helsinki Declaration of Human Rights, the Convention on Human Rights and Biomedicine of the Council of Europe, the laws of Ukraine, the regulations of the Ministry of Health of Ukraine, and the requirements of the Ethical Code of the Ukrainian Physician.

The analysis of cytokines (TNF-α, INFγ, IL-10) in cervical mucus was carried out by the method of enzyme-linked immunosorbent assay with corresponding standard commercial reagent kits of the company «Vector BEST» according to the manufacturer's instructions. The levels of the above-mentioned cytokines were determined at 5-6 weeks of gestation (at the beginning of gestational remodeling of the spiral arteries) and at 17-18 weeks of gestation (when trophoblast invasion into the vessel wall is complete). In addition, the cytokine profile of the studied women was examined separately at 32 weeks of pregnancy (the time when clinical manifestations of pre-eclampsia typically occur) [14]. The data obtained were processed using mathematical-statistical methods, calculating sample means (M), variance (σ) and standard errors of means (m). The Student's t-test was used for evaluation and the likelihood ratio was calculated using the «STATISTICA» software (StatSoft Inc., USA).

The paper is an excerpt from the initiative scientific research project of the Department of Obstetrics and Gynecology ¹ 2 of the Poltava State Medical University entitled «Optimization of approaches to pregnancy management in women at high risk of obstetric and perinatal pathology» (state registration number 0122U201228, duration: 10.2022-09.2027).

Results and Discussion

In group II pregnant women with CE, we observed a statistically significant increase in the levels of pro-inflammatory cytokines, which was already evident at 5-6 weeks of pregnancy and progressed over time. Specifically, in early pregnancy, the level of INF-γ was 2.1 times higher than the control values, reaching 62.8 ± 9.0 pg/mL (vs. 29.1 ± 4.1 pg/mL in the control group; p<0.001). At 17-18 weeks' gestation, this indicator was 80.8 ± 10.4 pg/mL (2.4 times higher than the control values (33.1 ± 5.2 pg/mL); p<0.001), and at 32 weeks' gestation, it was 38.8 ± 4.1 pg/mL. This was 1.7 times higher than in healthy pregnant women (22.2 ± 3.9 pg/ml; p<0.001). Similarly, TNF-α was 4.3 times higher than control levels at 5-6 weeks of pregnancy (88.1 ± 8.5 pg/ml vs. 20.4 ± 3.0 pg/ml; p<0.001), 3. 3 times at 17-18 weeks (96.8 ± 3.5 pg/ml vs. 29.2 ± 3.1 pg/ml; p<0.001) and 4.4 times at 32 weeks (100.7 ± 3.9 pg/ml vs. 22.4 ± 5.5 pg/ml; p<0.001).

Table 1

The level of pro- and anti-inflammatory cytokines in cervical mucus in pregnant women with a history of chronic endometritis

term	INF-γ (pg/ml)			TNFα (pg/ml)			IL-10 (pg/ml)		
	Control group n=20	Group I n=119	Group II n=116	Control group n=20	Group I n=119	Group II n=116	Control group n=20	Group I n=119	Group II n=116
5-6 weeks	29,1±4,1	33,4±4,8 p*>0,25	62,8±9,0 p*<0,001 p**<0,001	20,4±3,0	24,3±6,3 p*>0,5	88,1±8,5 p*<0,001 p**<0,001	25,6±2,9	28,3±2,7 p*>0,2	102,1±2,2 p*<0,0001 p**<0,0001
17-18 weeks	33,1±5,2	37,6±4,3 p*>0,5	80,8±10,4 p*<0,001 p**<0,001	29,2±3,1	36,6±4,6 p*>0,1	96,8±3,5 p*<0,001 p**<0,001	32,7±1,5	30,4±4,9 p*>0,5	104,0±4,1 p*<0,0001 p**<0,0001
32 week	22,2±3,9	26,8±3,6 p*>0,25	38,8±4,1 p*<0,001 p**<0,05	22,4±5,5	25,1±5,3 p*>0,5	100,7±3,9 p*<0,001 p**<0,001	27,3±3,9	27,9±5,1 p*>0,5	83,5±3,4 p*<0,0001 p**<0,0001

Note: p – from the CG in the same term; p**- in comparison with the Group I*

The increase in pro-inflammatory cytokine levels in group II women was accompanied by an increase in the concentration of anti-inflammatory IL-10. Specifically, the level of IL-10 in their cervical mucus was 102.1 ± 2.2 pg/ml at 5-6 weeks of pregnancy (4 times higher than the control values (25.6 ± 2.9 pg/ml; p<0.0001)); 104.0 ± 4. 1 pg/ml at 17-18 weeks' gestation (3.1-fold higher than in CG (32.7 ± 1.5 pg/ml; p<0.0001)) and 83.5 ± 3.4 pg/ml at 32 weeks' gestation (3-fold higher in the same comparison (27.3 ± 3.9 pg/ml; p<0.0001)). This counterbalances the increase in pro-inflammatory cytokines, allowing the TNF-alpha/IL-10 ratio to remain at levels characteristic of healthy women throughout pregnancy: 0.83 ± 0.06 at 5-6 weeks (compared to 0.8 ± 0.02 in CG (p>0.5)) and 0.93 ± 0.06 at 17-18 weeks (compared to 0.82 ± 0.04 in CG (p>0.1)).

Only at 32 weeks of gestation, in women with untreated CE, the TNF-alpha/IL-10 ratio increased to 1.2 ± 0.05 (p<0.001 vs. CG). This was associated with the fact that some women in this group had clinical manifestations of PE; this index increased to 1.93 ± 0.04 (p<0.0001 compared to CG). In the same patients whose pregnancy progressed without this complication, the TNF-α/IL-10 index was 0.94 ± 0.04, which was not significantly different from the values in the CG (p>0.5).

We found that the concentration of cytokines regulating invasive processes in the uterine spiral arteries (especially INF-γ and TNF-α) [16] was significantly higher in early pregnancy in women of group II, whose pregnancies were complicated by the development of preeclampsia in later stages. All women with an increase in INF-γ in cervical mucus greater than 66.4 pg/ml at 5-6 weeks' gestation subsequently developed PE (OR 2.01; 95 % CI [1.1-7.12]; p<0.05). An increase in TNF-α levels greater than 90.9 pg/ml in cervical mucus at this time also correlated with the manifestation of PE (OR 1.8; 95 % CI [1.2-6.29]; p<0.05).

At this time, the level of INF-γ in women in group II who later developed PE was 70.5±3.7 pg/mL at 5-6 weeks of gestation, which was 2.4 times higher than the level in healthy pregnant women in the control group (29.1±4.1 pg/mL; p<0.001). In group II women whose pregnancies were complicated by PE at later stages, TNF-α was 90.9±3.1 pg/ml at 5-6 weeks of pregnancy, which was 4.5 times higher than the levels in the control group (20.4±3.0 pg/ml; p<0.001).

However, the more pronounced the increase in proinflammatory cytokine levels, the more severe the PE

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tended to be during pregnancy. In patients in group II who developed severe PE at a later stage, INF-γ was 79.5 ± 3.0 pg/ml at the beginning of pregnancy. This was 20 % higher than in patients with moderate PE (66.4 ± 3.2 pg/ml; p<0.002), 34 % higher than in patients from group II whose pregnancies proceeded without PE (59.2 ± 4.3 pg/ml; p<0.001), and 2.7 times higher than in healthy pregnant women (29.1 ± 4.1 pg/ml; p<0.001). The change in TNF-α levels in cervical mucus at 5-6 weeks of pregnancy was less pronounced: in women with moderate pre-eclampsia, the level of this cytokine was 90.1 ± 2.8 pg/ml, which was 4.4 times higher than in healthy pregnant women (20.4 ± 3.0 pg/ml; p<0.001) and only 7 % higher than in patients from group II whose pregnancies proceeded without preeclampsia (83.8 ± 2.1 pg/ml; p>0.5). There was no significant difference in this indicator compared to patients with severe PE (93.4 ± 2.4 pg/ml; p>0.2). The level of TNF-α in cervical mucus was 4.5 times higher in women who developed severe PE at later stages compared to the control values (93.4 ± 2.4 pg/ml vs. 20.4 ± 3.0 pg/ml; p<0.01), whereas the levels were 11.4 % higher in women without PE (93.4 ± 2.4 pg/ml vs. 83.8 ± 2.1 pg/ml; p<0.01).

At 17-18 weeks' gestation, the level of INF-γ was 87.3 ± 2.8 pg/mL in group II women who later developed signs of PE, which was 2.6 times higher than the control values (33.1 ± 5.2 pg/mL; p<0.001) and 12 % higher than in group II women who did not develop pre-eclampsia during pregnancy (77.8 ± 3.3 pg/mL; p<0.05). In patients with severe pre-eclampsia, the concentration of this cytokine at 17-18 weeks' gestation was 8.4 % higher than in patients with moderate pre-eclampsia (p<0.02) and 20 % higher than in patients without pre-eclampsia (p<0.0002).

At 17-18 weeks' gestation, the level of TNF-α was 103.2±3.8 pg/mL in group II women whose pregnancies were subsequently complicated by pre-eclampsia, which was 3.5 times higher than in the control group (29.2±3.1 pg/mL; p<0.0001) and 13 % higher than in group II women whose pregnancies were without pre-eclampsia (91.5±2.3 pg/mL; p<0.01).

In all women in group II whose pregnancy progressed to the third trimester, including those who subsequently developed preeclampsia, the level of IL-10 in cervical mucus was high at both 5-6 weeks and 17-18 weeks of pregnancy and was significantly higher than the control values. Notably, the TNF-α/IL-10 ratio at this gestational age remained within normal limits both in women whose pregnancies were complicated by pre-eclampsia and in those who did not have such complications.

We observed an increase in the TNF-α/IL-10 index only at 32 weeks of gestation in women in group II who either had signs of pre-eclampsia at the time of examination or manifested it in the following weeks, which was 2.3 times higher than the control level (1.93 ± 0.04 vs. 0.83 ± 0.05; p<0.0001) and 2 times higher than the values in women who became pregnant with diagnosed CE but did not develop PE (0.94 ± 0.04; p<0.001).

The above changes were associated with an insufficient amount of IL-10 in patients with preeclampsia. At this time, in women of group II without pre-eclampsia, at 32 weeks of pregnancy, the values of this indicator (101.2 ± 4.1 pg/ml) increased by 3.7 times compared to the control values (27.3 ± 3.9 pg/ml), providing an adequate balance between pro- and anti-inflammatory cytokines (p<0.0001). However, in women with moderate pre-eclampsia, such an increase was 1.7 times higher (48.2 ± 2.3 pg/ml, p<0.01), and in women with severe pre-eclampsia, it was 1.5 times higher (43.1 ± 1.9; p<0.05). Consequently, the level of IL-10 was found to be 2.1 times lower in women with pre-eclampsia than in patients without such complications (46.3 ± 2.1 pg/ml vs. 101.2 ± 4.1 pg/ml; p<0.001), which is probably related to the depletion of compensatory mechanisms aimed at balancing Th1- and Th2-dependent cytokines. This indicates immunosuppression, which likely contributes to the development of endothelial dysfunction and subsequent manifestation of clinical symptoms of pre-eclampsia [21].

We evaluated the levels of TNF-α, INF-γ and IL-10 in cervical mucus of women treated for CE before pregnancy (group I). It was found that the level of INF-γ in treated women was 33.4±4.8 pg/mL at 5-6 weeks of pregnancy, 37.6±4.3 pg/mL at 17-18 weeks, and 26.8±3.6 pg/mL at 32 weeks. This was 1.8-fold (p<0.0001), 2.1-fold (p<0.0001) and 1.4-fold (p<0.0001) lower than in untreated patients, respectively. The values were not significantly different from those of healthy pregnant women (p>0.2 in all comparisons at the corresponding gestational ages). Similarly, TNF-α levels were lower than those observed in women in group II: by 3.6-fold at 5-6 weeks of pregnancy (24.3±6.3 pg/mL; p<0.01), by 2.6-fold at 17-18 weeks (36.6±4.6 pg/mL; p<0.0001), and by almost 4-fold at 32 weeks of pregnancy (25.1±5.3 pg/mL; p<0.001).

Apparently, preconception treatment for CE prevents the increased synthesis of pro-inflammatory cytokines, capable of inhibiting trophoblast invasion into the uterine spiral arteries both in the early weeks of pregnancy and later, avoiding excessive production of the anti-inflammatory cytokine IL-10. At 5-6 weeks of pregnancy, its level (28.3 ± 2.7 pg/ml) corresponds to that of healthy women (25.6 ± 2.9 pg/ml; p>0.2) and is 3.6 times (102.1 ± 2.2 pg/ml; p<0.0001) lower than in untreated patients of group II. At 17-18 weeks of pregnancy, the levels of this cytokine (30.4 ± 4.9 pg/mL) are almost similar to the control levels (32.7 ± 4.5; p>0.5) and 3.4 times lower compared to untreated women (p<0.0001). The TNF-α/IL-10 index was similar to control levels, at 0.85 ± 0.04 at the beginning of pregnancy (0.8 ± 0.02; p>0.2 in the control group) and 0.84 ± 0.08 in the second trimester (0.82 ± 0.04; p>0.5 in the control group). Stable levels of the anti-inflammatory cytokine in the first half of pregnancy prevent its depletion at 32 weeks' gestation, as observed in women in group II. The level of IL-10 in cervical mucus of women in group I at the same gestational age remains at the level typical for healthy patients (27.9 ± 5.1 pg/ml in group I vs. 27.3 ± 3.9 pg/ml in control group; p>0.5), and in group II this level is 2.9 times lower (83.5 ± 3.4 pg/ml; p<0.0001). Thus, the TNF-α/IL-10 ratio in treated women remains at the control level on average across groups (0.89 ± 0.1), whereas in untreated patients it increases to 1.2 ± 0.05 at 32 weeks' gestation (p<0.01), contributing to the clinical manifestations of complicated pregnancy.

In conclusion, in women with untreated CE, the production of cytokines that limit trophoblast invasion of the uterine spiral arteries increases in early pregnancy,

setting the stage for the development of pre-eclampsia. In women whose pregnancy occurred after comprehensive treatment of CE, the levels of these cytokines remain within normal ranges, promoting a physiological course of pregnancy in this group of women. This is evidenced by the significant difference in the clinical course of pregnancy between Group I and Group II women. The incidence of this complication was 17 % in group I women who received treatment in the preconception period and continued to receive medication and pre-eclampsia prophylaxis during pregnancy, compared with 32.1 % in untreated women (OR 2.3; 95 % CI [1.25-4.31]; p <0.05). Among them, moderate manifestations of this complication were observed in 17 women (85 % of cases among individuals in this group with pre-eclampsia), while in group II there were 27 women (73 % of 37 patients with pre-eclampsia; OR 2.51; 95 % CI [1.25-5.04]; p <0.05). Severe pre-eclampsia complicated pregnancy in 3 women in group I (15 % of women with pre-eclampsia) and in 10 women (27 % of women with pre-eclampsia) in group II (OR 4.64; 95 % CI [1.23-17.48]; p <0.05). The mean onset of pre-eclampsia was 34.3±0.4 weeks in group I and 29.4±0.6 weeks in group II.

Conclusions. The onset of pregnancy (5-6 weeks) in women with untreated chronic endometritis is accompanied by increased levels of cytokines (INF-γ by 2 times (p<0.001) and TNF-α by 4.3 times (p<0.001)) in cervical mucus that limit trophoblast invasion into the uterine spiral arteries. The priority of inhibitory cytokines that limit trophoblast invasion during the first wave of gestational transformation of the uterine spiral arteries is particularly pronounced in pregnant women whose further gestational process is complicated by the development of pre-eclampsia. An increase in INF-γ levels in cervical mucus greater than 66.4 pg/ml (OR 2.01; 95 % CI [1.1-7.12]; p<0.05) and an increase in TNF-α levels in cervical mucus greater than 90.9 pg/ml (OR 1. 8; 95 % CI [1.2-6.29]; p<0.05) at 5-6 weeks of gestation can be considered as predictors for the development of pre-eclampsia in women who became pregnant with chronic endometritis [23].

The level of IL-10 in cervical mucus at the beginning of pregnancy is 4 times higher in pregnant women with CE compared to the control level (p<0.0001). This is related to the need to maintain cytokine balance in the presence of high production of proinflammatory cytokines.

Women who received comprehensive pre-gravidar treatment for chronic endometritis before pregnancy have lower levels of antiinflammatory cytokines (INF-γ by 1.8 times (p<0.001); TNF-α by 3.6 times (p<0.001)) in cervical mucus at 5-6 weeks of gestation. This creates conditions for preventing the development of pre-eclampsia.

Comprehensive antepartum treatment and drug support during pregnancy, combined with protocol-based pre-eclampsia prevention measures in women with chronic endometritis, allow a 1.9-fold reduction in the incidence of this complication (OR 2. 3; 95 % CI [1.25-4.31]; p<0.05), a 1.8-fold reduction in the incidence of severe forms of pre-eclampsia (OR 4.64; 95 % CI [1.23-17.48]; p<0.05), and a 4.9-week delay in the mean onset of pre-eclampsia (p<0.0001) compared to untreated women.

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ЗМІНИ БАЛАНСУ ЦИТОКІНІВ У ВАГІТНИХ З ХРОНІЧНИМ ЕНДОМЕТРИТОМ В АНАМНЕЗІ ТА ЇХ РОЛЬ У ФОРМУВАННІ ПРЕЕКЛАМПСІЇ

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Резюме.

Існує дефіцит даних щодо рівнів TNF-α, INF-γ та IL-10 у цервікальному слизі жінок, які завагітніли на фоні хронічного ендометриту. Ці цитокіни впливають на перебіг вагітності та процеси інвазії трофобласта в спіральні артерії матки. Девіації їх рівнів на ранніх термінах вагітності можуть бути пов'язані з виникненням гестаційних ускладнень, зокрема з розвитком прееклампсії в більш віддалених термінах.

Мета і завдання дослідження: Вивчити рівень прозапальних (TNF, INF-γ) і протизапального (IL-10) цитокінів в слизі цервікального каналу у вагітних з хронічним ендометритом в анамнезі; визначити їх роль у формуванні прееклампсії; оцінити ефективність комплексного преконцепційного лікування у попередженні цитокінового дисбалансу і профілактиці гестаційних ускладнень.

Матеріал та методи дослідження. Спостерігали за перебігом вагітності у 135 жінок, які до мали хронічний ендометрит в анамнезі і преконцепційно отримували його лікування (I група), та у 168 пацієнток, вагітність яких настала на фоні нелікованого хронічного ендометриту (II група). Групу контролю склали 20 здорових пацієнток. Преконцепційне лікування включало призначення азитроміцину, гормональну терапію препаратом фемостон 2/10 та L-аргініна аспартат на фоні фолатопрофілактики.

При виконанні досліджень керувались Правилами гуманного ставлення до пацієнта згідно з вимогами Токійської декларації Всесвітньої медичної асоціації, Міжнародними рекомендаціями Гельсинської декларації з прав людини, Конвенцією Ради Європи щодо прав людини і біомедицини, Законами України, наказами МОЗ України та вимогами Етичного Кодексу лікаря України.

Дослідження цитокінів (TNF-α, INFγ, ІЛ-10) у цервікальному слизі в 5-6 тижнів, в 17-18 та в 32 тижні вагітності проводили методом імуноферментного аналізу. Показники статистично обробляли з розрахунком середніх вибіркових значень (M),

дисперсії (σ) та помилок середніх значень (m), оцінкою критерію Ст'юдента та розрахунку вірогідності шансів за допомогою програми «STATISTICA» («StatSoft Inc.», США).

Стаття є фрагментом ініціативної НДР кафедри акушерства і гінекології № 2 Полтавського державного медичного університету «Оптимізація підходів до ведення вагітності у жінок груп високого ризику по виникненню акушерської та перинатальної патології» (№ держреєстрації 0122U201228, термін виконання 10.2022-09.2027).

Результати дослідження. У вагітних з хронічним ендометритом в анамнезі має місце збільшення кількості INF-γ в цервікальному слизі в 2,1 рази в 5-6 тижнів (p<0,001), в 2,4 рази в 17-18 тижнів (p<0,001) та в 1,7 разів в 32 тижні вагітності (p<0,001) порівняно з відповідними рівнями цього цитокіну у здорових вагітних. Аналогічно TNF-α перевищував значення в ГК у 4,3 рази в терміні 5-6 тижнів вагітності (p<0,001), в 3,3 рази – в терміні 17-18 тижнів (p<0,001) та в 4,4 рази – в 32 тижні (p<0,001). Усі вагітні з хронічним ендометритом в анамнезі, які в 5-6 тижнів вагітності мали в цервікальному слизі рівень INF-γ більше 66,4 пг/мл і/або рівеньTNF-α – більше 90,9 пг/мл, в подальшому мали маніфестацію прееклампсії (ВШ 2,01; ДІ 95 % [1,1-7,12]; p<0,05 і ВШ 1,8; ДІ 95 % [1,2-6,29]; p<0,05 відповідно). При цьому, чим більш виразним було зростання рівнів прозапальних цитокінів, тим більш тяжкою виявилася ПЕ в перспективі гестаційного процесу. Рівень IL-10 у їх цервікальному слизі був вище контрольних значень у 4 рази в 5-6 тижнів вагітності (p<0,0001)); у 3,1 рази у 17-18 тижнів (p<0,0001), та у 3 рази в 32 тижні (p<0,0001). У пролікованих жінок концентрація INF-γ є меншою, ніж у нелікованих пацієнток в 1,8 рази в 5-6 тижнів вагітності (p<0,0001), в 2,1 рази в 17-18 тижнів (p<0,0001), та в 1,4 рази в 32 тижні (p<0,0001). Аналогічно TNF-α в цервікальному слизі виявився нижчими в 3,6 рази (p<0,01), в 2,6 рази (p<0,0001) та в 4 рази (p<0,001) відповідно у зазначені терміни

Висновки. У жінок, що завагітніли на фоні нелікованого хронічного ендометриту, на ранніх етапах вагітності збільшується вироблення цитокінів INF-γ і TNF-α, які лімітують процеси інвазії трофобласту в спіральні артерії матки і створюють передумови для формування прееклампсії. Комплексне прегравідарне лікування хронічного ендометриту дає можливість нормалізувати рівні протизапальних цитокінів INF-γ та TNF-α на початку гестації, що створює передумови для запобігання розвитку прееклампсії. Це дає можливість зменшити частоту виникнення цього ускладнення в 1,9 рази (ВШ 2,3; ДІ 95 % [1,25-4,31]; p<0,05), знизити частоту тяжких форм прееклампсії в 1,8 разів (ВШ 4,64; ДІ 95 % [1,23-17,48]; p <0,05), відтермінувати середній термін маніфестації її проявів на 4,9 тижнів (p<0,0001).

Ключові слова: пре еклампсія; хронічний ендометрит; INF-γ; TNF-α; інвазія трофобласта в спіральні артерії матки.

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