UDC: 618.39-021.3618.14-002
DOI: 10.24061/2413-4260. XIV.2.52.2024.9

PREREQUISITES FOR EARLY PREGNANCY LOSS IN WOMEN WITH CHRONIC ENDOMETRITIS

***V. Likhachov*[1], *O. Taranovska*[1], *I. Zhabchenko*[2], *V. Oksiuta*[3], *V. Palapa*[3], *E. Krutikova*[1]**

Poltava State Medical University[1] (Poltava, Ukraine), SE «Institute of Pediatrics, Obstetrics and Gynecology named after acad. O. M. Lukyanova of the NAMS of Ukraine»[2] (Kyiv, Ukraine)
[3]Communal Institution of Higher Education «Rivne Medical Academy « of the Rivne Regional Council Ministry of Health of Ukraine (Rivne, Ukraine)

Summary

The incidence of chronic endometritis is particularly high in women with spontaneous abortions, especially habitual ones. There are insufficient data on the mechanisms of miscarriage in women whose pregnancy occurred along with this pathology.

***Aim:** to assess the level of synthesis of cytokines and endometrial proteins in women with CE in the preconceptional stage and in the early stages of pregnancy; to identify pathogenetic aspects of the impact of imbalance of these substances on the processes of pregnancy loss; to assess the possibility of correcting the identified changes in the preconceptional stage.*

***Materials and methods.** The study was conducted in 2 phases. In the first phase, 426 women with CE were studied (168 patients (group I) were treated for CE in the preconception period, and the rest, 258 patients (group II), did not receive treatment). The control group consisted of 30 healthy women. The levels of cytokines TNF-a, INF-γ, and IL-10 in cervical mucus and glycodelin in menstrual blood were determined by enzyme-linked immunosorbent assay. In the second phase of the study, women who became pregnant were followed: 135 women from group I who received preconceptional treatment for CE; 168 women from group II who became pregnant along with untreated CE; and 20 healthy women from the control group who became pregnant and subsequently had no complications. At 5-6 weeks of gestation, serum glycodelin concentration and cervical content levels of TNF-a, INF-γ and IL-10 were determined. The data were processed using mathematical statistical methods, Student's t-test, Pearson's correlation coefficient (r) and odds ratio were evaluated using the STATISTICA program of StatSoft Inc. (USA). The study adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee of PSMU for all women enrolled in this study.*

The article is extracted from the initiative scientific research project of the Obstetrics and Gynecology Department No 2 of the Poltava State Medical University «Optimization of approaches to pregnancy management in women at high risk of obstetric and perinatal pathology» (term: 2022-2027; state registration number 0122U201228).

***Results and Discussion.** At the preconceptional stage, patients with CE showed a significant decrease in glycodelin levels by 2.9 times ($p<0.05$), an increase in proinflammatory cytokines (INF-γ by 2.8 times ($p<0.001$), TNF-α by half ($p<0.001$)), and a decrease in IL-10 by 2 times ($p<0.001$) compared to the levels in healthy non-pregnant women. A decrease in the level of glycodelin in menstrual blood of women with CE is inversely correlated with an increase in the level of proinflammatory cytokines in cervical mucus (both INF-γ; $r= –0.77$; $p<0.05$, and TNF-α; $r= –0.69$; $p<0.05$). At 5-6 weeks of gestation, the level of serum glycodelin was 14.5 % lower ($p<0.05$) in patients with pregestational untreated CE and 58.6 % lower ($p<0.001$) in women with early pregnancy loss. The level of this protein in menstrual blood of women with CE before pregnancy was positively correlated with its concentration in serum at 5-6 weeks of pregnancy ($r=0.61$; $p<0.01$). Such a relationship was also characteristic for INF-γ ($r=0.68$; $p<0.05$) and TNF-α ($r=0.78$; $p<0.05$). An inverse correlation was also found between a decrease in glycodelin levels in the blood of pregnant women with a history of untreated CE at 5-6 weeks of pregnancy and an increase in TNF-α ($r= –0.63$; $p<0.05$) and INF-γ ($r= –0.57$; $p<0.05$) in the cervical mucus of these pregnant women at this stage of pregnancy. After treatment for CE, both in the preconceptional stage and in early pregnancy, an increase in glycodelin ($p<0.001$), a decrease in INF-γ ($p<0.05$) and TNF-α ($p<0.01$), and an increase in IL-10 concentration ($p>0.05$) were observed. The incidence of spontaneous abortion before 22 weeks' gestation decreased 1.9-fold in women who received preconception treatment (OR 2.79; CI 95 % [1.45-5.38]; $p < 0.05$).*

***Conclusions.** In women with CE, there is a decrease in glycodelin synthesis and cytokine imbalance with an increase in proinflammatory cytokines: INF-γ (2.8-fold; $p>0.001$) and TNF-α (twofold; $p<0.001$). The preconceptional decrease in glycodelin synthesis correlates with a decrease in synthesis of this protein by decidual cells after pregnancy, as well as with the prevalence of INF-γ and TNF-α in early pregnancy in women with a history of CE. This sets the stage for impaired immune tolerance between the uterus and the fetus and is one of the leading causes of spontaneous abortion in women who become pregnant with untreated CE. Preconceptional treatment of CE prevents the formation of cytokine imbalance and increases glycodelin synthesis in the early stages of pregnancy, which protects the course of pregnancy and reduces the incidence of early preterm labor by 4.6 times.*

***Key words:** Chronic Endometritis; Spontaneous Abortion; Glycodelin; INF-γ; TNF-α.*

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

Introduction

In recent years, the incidence of spontaneous abortion has been steadily increasing, mainly due to the uterine factor [1, 2]. Thus, according to studies conducted in 2021-2023, on average, up to 43 % of reproductive problems are associated with pathological processes of the endometrium [3,4]. And the incidence of chronic endometritis (CE) is 2 times higher than the prevalence of other forms of uterine pathology [5,6]. In patients with recurrent pregnancy loss, the incidence of this pathology reaches 33 % to 87 % [7,8].

The cause of early pregnancy loss in CE may be the secondary histopathologic changes in the endometrium as a result of a prolonged inflammatory process [9]. They are most often manifested by local stromal edema, increased stromal cell density, glandular destruction, and the presence of plasma cell infiltration in the endometrial stroma [9, 10, 11], which leads to disrupted receptivity of the uterine mucosa and its cyclic transformation during the menstrual cycle [11]. The consequence of such changes is a decrease in the synthesis of specific endometrial proteins whose role is to prepare the endometrium for implantation [12].

One of these proteins is glycodelin (α2-microglobulin fertility, AMGF). It is synthesized by the epithelium of the endometrial glands in the second phase of the menstrual cycle under the stimulating effect of progesterone [13]. Its levels increase during the «implantation window» and remain high until the onset of the next menstrual period and during the first days of the next cycle [10,12]. In the case of pregnancy, glycodelin synthesis continues and its level in the decidual tissue increases steadily during the first trimester [9,13]. An important function of glycodelin is to transport hydrophobic molecules necessary for embryonic development from the tissue environment [13]. In addition, this protein protects the embryo from the immune response of the mother's body [13]. In case of protein deficiency, the synthesis of the proinflammatory cytokines TNF-α and INF-γ by monocytes and macrophages is activated [14, 15].

It is now known that successful pregnancy requires the dominance of a Th-2 mediated immune response between maternal and fetal tissues, which provides relative immunosuppression through increased synthesis of anti-inflammatory cytokines, including IL-10 [15]. This cytokine prepares the endometrium for implantation and limits the activity of natural killer cells and macrophages [16]. The predominance of Th-1-mediated immunological reactions between maternal and fetal tissues initiates the production of proinflammatory cytokines such as INF-γ, tumor necrosis factor alpha (TNF-α) and interleukins IL-1, IL-2, IL-12, IL-15, IL-18 by decidual macrophages [17,18]. To date, the proinflammatory cytokines TNF-α and INF-γ are known to have a direct cytotoxic effect on fetal cells [16], as well as to contribute to endothelial dysfunction [19], chorionic vascular thrombosis, fetal oocyte death, and oocyte rejection [15, 20].

The presence of a cytokine imbalance in the endometrium in CE negatively affects the course of pregnancy and causes a high incidence of abortion. However, the mechanisms of this effect are not well understood, and new studies are needed in both the preconceptional and gestational periods.

Aim: to assess the level of synthesis of cytokines and endometrial proteins in women with CE in the preconceptional stage and in the early stages of pregnancy; to identify pathogenetic aspects of the impact of imbalance of these substances on the processes of pregnancy loss; to assess the possibility of correcting the identified changes in the preconceptional stage.

Materials and methods. The study was conducted in 2 phases. In the first, preconceptional stage, 426 women with CF who were planning a pregnancy were examined. The balance of proinflammatory cytokines (TNF-α, та INF-γ) and anti-inflammatory interleukin IL-10 was estimated by enzyme-linked immunosorbent assay in cervical mucus on days 5-10 of the menstrual cycle. The level of glycodelin protein (α-2-microglobulin of fertility) in menstrual blood was evaluated by enzyme-linked immunosorbent assay.

Of the women studied, 168 patients (group I) were treated in the preconceptional period with azithromycin (1 g on the first day of menstruation, followed by 500 mg daily for a total of 5 days), femostone-2/10 (3 months continuously), and L-arginine (6 g orally for 2 months). After treatment, women in group I were reassessed to evaluate the efficacy of the therapy. The remaining 258 patients did not receive pre-gravid treatment for CE and formed Group II. The control group (CG) consisted of 30 healthy women without CE or other reproductive problems.

In the second phase of the study, women who became pregnant were followed. There were 323 such patients: 135 women from Group I (i.e., those who received a specific pre-pregnancy treatment for CE); 168 women from Group II (whose pregnancy occurred along with untreated CE); and 20 healthy women from the control group who became pregnant and subsequently had no complications. At the beginning of pregnancy (5-6 weeks), these women underwent repeated determination of the levels of the cytokines TNF-α, INF-γ and IL-10 in the cervical contents, as well as the serum concentration of glycodelin.

The obtained data were processed using mathematical statistical methods, calculating sample means (M), variance (σ), and errors of the mean (m); Student's t-test was evaluated, Pearson's paired correlation coefficient (r) was determined, and the probability of odds was calculated. The STATISTICA software from StatSoft Inc. (USA) was used in the study. All studies were conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee of PSMU for all women enrolled in this study.

The article is extracted from the initiative scientific research project of the Obstetrics and Gynecology Department No 2 of the Poltava State Medical University «Optimization of approaches to pregnancy management in women at high risk of obstetric and perinatal pathology» (term: 2022-2027; state registration number 0122U201228).

Results and Discussion

At the preconceptional stage, a significant decrease in glycodelin levels was found in patients with CE compared to CG. In women with CE, it was 13.7±3.6 μg/mL, which was 2.9 times lower than in controls (39.8±8.3 μg/mL; $p<0.05$). In addition, these patients showed increased levels of proinflammatory cytokines. Thus, the concentration of INF-γ in women with CE reached 8.3+1.2 pg/mL, which was 2.8 times ($p<0.001$) higher than the control values (2.93±1.2 pg/mL). The level of TNF-α was also doubled in this comparison: 3.4+0.23 pg/mL in women with CE vs. 1.61±0.13 pg/mL ($p<0.001$) in the control group.

However, the level of IL-10 was 2 times lower in women with CE: 4.2+0.6 pg/mL vs. 8.83+0.14 pg/mL in healthy non-pregnant women ($p<0.001$). Correlation analysis revealed that a decrease in menstrual glycodelin levels was inversely correlated with an increase in cervical mucus proinflammatory cytokines (both INF-γ; $r= –0.77$; $p<0.05$, and TNF-α; $r= –0.69$; $p<0.05$). We hypothesize that in CE morphofunctional changes in the uterine mucosa, manifested by a decrease in the intensity of synthesis of proteins necessary for preparation for implantation by its glands, are associated with the formation of cytokine imbalance and potentiate the prevalence of proinflammatory cytokines. Obviously, pregnancy under such conditions is at high risk of pregnancy complications, primarily miscarriage.

Finally, out of 168 women who became pregnant with untreated CE, 41 women (24.4 %) had a spontaneous abortion before 22 weeks. This occurred most frequently in the early stages of pregnancy (up to 8 weeks): 56 % of all miscarriages occurred at this time (in 23 women).

In order to identify the mechanisms of influence of the detected preconceptional changes on the increase in miscarriage incidence, we continued to follow the women after pregnancy (stage 2 of the study). It was found that at 5-6 weeks of gestation in patients with pregestational untreated CE, the level of serum glycodelin accounted for 131.6±6.6 ng/mL, which was by 14.5 % lower than the corresponding level in CG (154.1±7.12 ng/mL; $p<0.05$). Serum glycodelin levels were also calculated in untreated women who lost pregnancy at an early stage (up to 8 weeks). At 5-6 weeks of gestation, glycodelin levels were 58.6 % lower than in controls, which is dramatically low for this gestational age (90.3±6.91 ng/ml; $p<0.001$). At the same time, a significant positive correlation was found between the level of this protein in the menstrual blood of women with CE before pregnancy and its concentration in the women's serum at 5-6 weeks of pregnancy ($r=0.61$; $p<0.01$). This led us to conclude that untreated CE during pregnancy causes a decrease in glycodelin synthesis by decidual cells, leading to a high incidence of spontaneous abortion in such patients.

Changes in the secretory function of the decidua were accompanied by shifts in the cytokine profile of untreated pregnant women with a history of CE. Thus, the level of INF-γ in cervical mucus at the beginning of pregnancy exceeded the control level by 2.12 times (62.79±9.0 pg/ml vs. 29.12±4.1 pg/ml in healthy pregnant women at the same gestational age ($p<0.001$). The level of TNF-α was 4.3 times higher compared to the levels in CG (88.12±8.49 pg/mL vs. 20.41±3.0 pg/mL; $p<0.001$). The levels of TNF-α at 5-6 weeks of gestation in women with a history of CE were positively correlated with the levels of this indicator at the stage of pregnancy preparation ($r=0.78$; $p<0.05$). This correlation was also characteristic of INF-γ levels ($r=0.68$; $p<0.05$). In addition, an inverse correlation was found between a decrease in glycodelin levels in the blood of pregnant women with a history of untreated CE at 5-6 weeks of pregnancy and an increase in TNF-α ($r= –0.63$; $p<0.05$) and INF-γ ($r= –0.57$; $p<0.05$) in the cervical mucus of these pregnant women at the same term of pregnancy.

An increase in proinflammatory cytokines in the early stages of pregnancy that occurred in CE was accompanied by an increase in the anti-inflammatory cytokine IL-10. However, this was only characteristic of patients whose pregnancies progressed. In them, the level of this cytokine was 102.1±2.2 pg/ml, which was 4 times higher than in healthy women at the same stage of pregnancy (25.6±2.9 pg/ml; $p<0.0001$). In 23 patients who lost pregnancy in the first trimester, the level of this indicator at the beginning of pregnancy was 2 times lower (13.0±3.4 pg/ml) ($p<0.001$ compared with the control level), although the concentration of TNF-α (89.6±2.5 pg/ml) and INF-γ (64.1±4.8 pg/ml) in these women did not differ significantly from that in the patients of group II as a whole. In our opinion, it was the imbalance with the predominance of proinflammatory cytokines that caused the high incidence of pregnancy loss in women who became pregnant with preconceptionally untreated CE. The property of these cytokines is the initiation of Th1-dependent immunological responses that provoke the death of the fetal oocyte and its expulsion from the uterine cavity [14,15,16,18].

Apparently, in such conditions there is a need for adequate pre-gravid preparation, which should compensate for the negative effects of this pathology on the endometrial readiness for implantation and on the further functional capacity of the decidual cast. Taking into account the identified changes, we developed a complex containing broad-spectrum antibacterial agents, hormonal agents to restore endometrial receptivity and synthetic function, and L-arginine to improve endometrial blood flow. After preconception treatment with CE in women of group I, we observed an increase in glycodelin in menstrual blood to 34.6±6.9 μg/ml. This is 2.5 times higher than the baseline values before treatment (13.7±3.6 μg/ml; $p<0.001$). The levels of proinflammatory cytokines in cervical mucus decreased: INF-γ in women after treatment accounted for 3.2±1.6 pg/ml, which was 2.6 times lower compared to the baseline before treatment (8.4±1.4 pg/ml; $p<0.05$). The level of TNF-α was also reduced by half (from 3.6±0.5 pg/mL before treatment to 1.8±0.3 pg/mL after treatment; $p<0.01$). On the contrary, the concentration of IL-10 increased by 72 % during treatment (from 4.4±0.8 pg/mL to 7.6±1.2 pg/mL; $p<0.05$), which is not significantly different from the level of controls (8.83±1.42 pg/mL; $p>0.05$).

After the onset of pregnancy, the serum level of glycodelin (152.5±7.3 ng/ml) at 5-6 weeks of gestation was 15.9 % higher than in the group of untreated patients ($p<0.05$). The level of INF-γ in cervical mucus of these

patients (33.4±4.8 pg/ml) was 1.8 times lower than in untreated women ($p<0.0001$), and the level of TNF-α (24.3±6.3 pg/ml) was 3.6 times lower ($p<0.01$). Instead, the level of the anti-inflammatory cytokine IL-10 (28.3 ± 2.7 pg/ml) did not increase as in pregnant women with a history of untreated CE, but remained within the limits inherent to healthy women (25.6 ± 2.9 pg/ml, $p>0.2$). At the same time, it was 3.61 times lower than the level in the group of untreated women before pregnancy ($p>0.0001$).

Consequently, the incidence of spontaneous abortion before 22 weeks of pregnancy decreased by 1.9 times in women who received preconceptional treatment (OR 2.79; CI 95 % [1.45-5.38]; $p < 0.05$), and the incidence of early pregnancy loss (up to 8 weeks) decreased by 4.6 times (13.7 % of this pathology in the cohort of women untreated before pregnancy vs. 2.96 % among those who received preconceptional treatment (OR 5.21; CI 95 % [1.75-15.42] $p < 0.05$).

Conclusions

1. In non-pregnant women with untreated CE, glycodelin synthesis decreased by 2.4-fold, which was accompanied by a cytokine imbalance with increased production of proinflammatory cytokines: INF-γ (2.8-fold; $p>0.001$) and TNF-α (twofold; $p<0.001$).

2. The preconceptional decrease in the synthesis of a specific protein glycodelin by the endometrial glands is correlated with a decrease in the synthesis of this protein by the decidual cells after pregnancy, as well as with an increase in their production of INF-γ and TNF-α, which occurs in the early stages of pregnancy in women with a history of CE. This creates the conditions for a violation of immunological tolerance between the uterus and the fetus and is one of the leading causes of spontaneous abortion in women who become pregnant with untreated CE.

3. Our proposed treatment of CE at the stage of preconceptional preparation prevents the formation of cytokine imbalance and increases the synthesis of glycodelin in the early stages of pregnancy, which protects the course of pregnancy and reduces the incidence of early pregnancy loss by 4.6 times.

References:

1. Cao C, Bai S, Zhang J, Sun X, Meng A, Chen H. Understanding recurrent pregnancy loss: recent advances on its etiology, clinical diagnosis, and management. Med Rev. 2022;2(6):570-89. doi: 10.1515/mr-2022-0030

2. Pirtea P, Cicinelli E, De Nola R, de Ziegler D, Ayoubi JM. Endometrial causes of recurrent pregnancy losses: endometriosis, adenomyosis, and chronic endometritis. Fertil Steril. 2021;115(3):546-60. doi: 10.1016/j.fertnstert.2020.12.010

3. La X, Wang W, Zhang M, Liang L. Definition and multiple factors of recurrent spontaneous abortion. Adv Exp Med Biol. 2021;1300:231-57. doi: 10.1007/978-981-33-4187-6_11

4. Huang CC, Hsueh YW, Chang CW, Hsu HC, Yang TC, Lin WC, et al. Establishment of the fetal-maternal interface: developmental events in human implantation and placentation. Front Cell Dev Biol[Internet]. 2023[cited 2024 Mar 17];11:1200330. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2023.1200330/full doi: 10.3389/fcell.2023.1200330

5. Deng T, Liao X, Zhu S. Recent advances in treatment of recurrent spontaneous abortion. Obstet Gynecol Surv. 2022;77(6):355-66. doi 10.1097/OGX.0000000000001033

6. Kuroda K, Horikawa T, Moriyama A, Nakao K, Juen H, Takamizawa S, et al. Impact of chronic endometritis on endometrial receptivity analysis results and pregnancu outcomes. Immun Inflamm Dis. 2020;8(4):650-8. doi: 10.1002/iid3.354

7. Gu J, Sun Q, Qi Y, Hu F, Cao Y. The effect of chronic endometriris and treatment on patients with unexplained infertility. BMC Womens Health. 2023;23(1):345. doi: 10.1186/s12905-023-02499-6

8. Xu Y, Mei J, Diao L, Li Y, Ding L. Chronic endometritis and reproductive failure: role of syndecan-1. Am J Reprod Immunol[Internet]. 2020[cited 2024 Mar 17];84(3): e13255. Available from: https://onlinelibrary.wiley.com/doi/10.1111/aji.13255 doi: 10.1111/aji.13255

9. Hirata K, Kimura F, Nakamura A, Kitazawa J, Morimune A, Hanada T, et al. Histological diagnostic criterion for chronic endometritis based on the clinical outcomes. BMC Womens Health. 2021;21(1):94. doi: 10.1186/s12905-021-01239-y

10. Pérez-Cejuela BA, Vitale SG, Pérez-Medina T, Rios-Vallejo M, Della Corte L, Vicente AR, et al. Hysteroscopic versus histopathological agreement in the diagnosis of chronic endometritis: results from a retrospective observational study. Arch Gynecol Obstet. 2023;308(6):1817-22. doi: 10.1007/s00404-023-07163-w

11. Puente E, Alonso L, Laganà AS, Ghezzi F, Casarin J, Carugno J. Chronic endometritis: old problem, novel insights and future challenges. Int J Fertil Steril. 2020;13(4):250-6. doi: 10.22074/ijfs.2020.5779

12. Löb S, Vattai A, Kuhn C, Schmoeckel E, Mahner S, Achim W, et al. Pregnancy Zone Protein (PZP) is significantly upregulated in the deciduas of recurrent and spontaneous miscarriage and negatively correlated to Glycodelin A (GdA). J Reprod Immunol [Internet]. 2021[cited 2024 Mar 1];143:103267. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0165037820301881?via%3Dihub doi: 10.1016/j.jri.2020.103267

13. Taranovska OO, Likhachov VK, Dobrovolska LM, Makarov OG, Shymanska YV. The role of secreting function of deciduas in the development of complications of gestation process in pregnant women with a past history of chronic endometritis. Wiad Lek. 2020;73(11):2416-20.

14. Lee CL, Chiu PC, Lam KK, Siu SO, Chu IK, Koistinen R, et al. Differential actions of glycodenin-A on Th-1 and Th-2 cell: a paracline mechanism that could produce the Th-2 dominant environment during pregnancy. Hum Reprod. 2011;26(3):517-26. doi: 10.1093/humrep/deq381

15. Li D, Zheng L, Zhao D, Xu Y, Wang Y. The role of immune cells in recurrent spontaneous abortion. Reprod Sci. 2021;28(12):3303-15. doi: 10.1007/s43032-021-00599-y

16. Komsa-Penkova R, Danailova A, Krumova S, Georgieva G, Giosheva I, Gartcheva L, et al. Altered thermal behavior of blood plasma proteome related to inflammatory cytokines in early pregnancy loss. Int J Mol Sci[Internet]. 2022[cited 2024 Apr 16];23(15):8764. Available from: https://www.mdpi.com/1422-0067/23/15/8764 doi: 10.3390/ijms23158764

17. Likhachov V, Taranovska O. Changes in cytokine balance in pregnant women with chronic endometritis in the past medical history and their role in the development of preeclampsia. Neonatology, Surgery and Perinatal Medicine. 2023;13(4):111-6. doi: 10.24061/2413-4260.XIII.4.50.2023.16

18. Wang W, Sung N, Gilman-Sachs A, Kwak-Kim J. T Helper (Th) cell profiles in pregnancy and recurrent pregnancy losses: Th1/Th2/Th9/Th17/Th22/Tfh cells. Front Immunol[Internet]. 2020[cited 2024 Apr 16];11:32025. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2020.02025/full doi: 10.3389/fimmu.2020.02025

19. Chekalina NI, Kazakov YM, Mamontova TV, Vesnina LE, Kaidashev IP. Resveratrol more effectively than quercetin reduces endothelium degeneration and level of necrosis factors α in patients with coronary artery disease. Wiad Lek. 2016;69(3pt2):475-9.

20. Begum A, Mishra A, Das CR, Das S, Dutta R, Kashyap N, et al. Impact of TNF-α profile in recurrent pregnancy loss pathogenesis: a patient based study from Assam. J Reprod Immunol[Internet]. 2021[cited 2024 Apr 1];148:103430. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0165037821001601?via%3Dihub doi: 10.1016/j.jri.2021.103430

ПЕРЕДУМОВИ САМОВІЛЬНОГО ВИКИДНЯ В РАННІХ ТЕРМІНАХ ВАГІТНОСТІ, ЩО НАСТАЛАЛА НА ФОНІ ХРОНІЧНОГО ЕНДОМЕТРИТУ

***В.Ліхачов*[1], *О.Тарановська*[1], *І.Жабченко*[2], *В.Оксюта*[3], *В.Палапа*[3], *Е.Крутікова*[1]**

Полтавський державний медичний університет[1]
(м. Полтава, Україна),
ДУ «Інститут педіатрії, акушерства і гінекології ім. акад. О. М. Лук'янової НАМН України»[2]
(м. Київ, Україна),
Комунальний заклад вищої освіти «Рівненська медична академія» Рівненської обласної ради МОЗ України[3]
(м. Рівне, Україна)

Резюме.

Частота хронічного ендометриту є особливо високою у жінок з самовільним викиднем, особливо звичним. Не достатньо даних про механізми викидня у жінок, вагітність яких настала на фоні цієї патології.

Мета і завдання дослідження: оцінити рівень синтезу цитокінів та ендометріальних білків у жінок з ХЕ на преконцепційному етапі та на початкових термінах гестації; виявити патогенетичні аспекти впливу дисбалансу цих речовин на процеси переривання вагітності; оцінити можливості корекції виявлених змін на етапі преконцепційної підготовки.

Матеріали та методи дослідження. Дослідження було проведене в 2 етапи. На першому етапі було обстежено 426 жінок з ХЕ (з них 168 пацієнток (I група) на преконцепційному етапі лікували ХЕ, решта, 258 пацієнток (II група), не отримували лікування). В контрольну групу були включені 30 здорових жінок. Визначали кількість цитокінів TNF-α, INF-γ, та IL-10 в цервікальному слизі та глікоделіна у менструальній крові методом імуноферментного аналізу На 2 етапі дослідження продовжувалося спостереження за тими з обстежених жінок, у яких настала вагітність: 135 жінок з групи I, хто отримав преконцепційне лікування ХЕ; 168 жінок з групи II, вагітність у яких настала на фоні нелікованого ХЕ, а також 20 здорових жінок з групи контролю, у яких вагітність настала і в подальшому протікала без ускладнень. В 5-6 тижнів вагітності визначали сироваткову концентрацію глікоделіну та рівень TNF-α, INF-γ та IL-10 в шийковому вмісті і. Дані обробляли з використанням методів математичної статистики, оцінювали критерій Ст'юдента, коефіцієнт парної кореляції (r) Пірсона, вірогідність шансів за допомогою програми «STATISTICA» «StatSoft Inc.» (США). В дослідженні дотримувалися положень Гельсинської Декларації. Протокол дослідження узгоджений Локальним етичним комітетом ПДМУ. для усіх жінок, хто брав участь у даному дослідженні.

Робота є частиною 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», (термін виконання 2022-2027 рр.; № державної реєстрації 0122U201228).

Результати та їх обговорення. На преконцепційному етапі у пацієнток з ХЕ було виявлене достовірне зменшення рівня глікоделіну в 2,9 рази ($p<0,05$), зростання рівнів прозапальних цитокінів (INF-γ у 2,8 рази ($p<0,001$), TNF-α вдвічі ($p<0,001$)), зменшення кількості IL-10 в 2 рази ($p<0,001$) порівняно з рівнями у здорових невагітних жінок. Зменшення рівня глікоделіну в менструальній крові жінок з ХЕ обернено корелює зі зростанням вмісту прозапальних цитокінів в цервікальному слизі (як INF-γ; $r= –0,77$; $p<0,05$, так і TNF-α; $r= –0,69$; $p<0,05$). В 5-6 тижневому терміні вагітності у пацієнток, що мали нелікований догестаційно ХЕ, рівень сироваткового глікоделіну був на 14,5 % є меншим ($p<0,05$), а тих з них, які втратили вагітність на ранніх термінах – 58,6 % меншим ($p<0,001$). Рівень цього білка в менструальній крові у жінок з ХЕ до вагітності позитивно корелював з його концентрацією у цих жінок в сироватці крові в 5-6 тижнів вагітності ($r=0,61$; $p<0,01$). Такий зв'язок був характерний і для рівнів INF-γ ($r=0,68$; $p<0,05$), і для TNF-α ($r=0,78$; $p<0,05$). Була також виявлена обернена кореляція між падінням рівня глікоделіну у крові вагітних з нелікованим ХЕ в анамнезі в 5-6 тижнів вагітності та зростанням TNF-α ($r= –0,63$; $p<0,05$) і INF-γ ($r= –0,57$; $p<0,05$) у цервікальному слизі цих вагітних в даному терміні. Після проведеного лікування ХЕ, як на преконцепційному етапі, так і на ранніх термінах вагітності відмічалося зростання глікоделіну ($p<0,001$), зменшення вмісту INF ($p<0,05$) та TNF-α ($p<0,01$) та збільшення концентрації IL-10 ($p>0,05$). Частота самовільного викидня до 22 тижнів вагітності у жінок, що отримували преконцепційне лікування зменшилася в 1,9 рази (ВШ 2,79; ДІ 95 % [1,45-5,38]; $p <0,05$),

Висновки. У жінок ХЕ має місце зменшення синтезу глікоделіну і цитокіновий дисбаланс зі зростанням прозапальних цитокінів: INF-γ (в 2,8 разів; $p>0,001$) і TNF-α (вдвічі; $p<0,001$). Преконцепційне зменшення синтезу глікоделіну корелятивно пов'язане зі зменшенням синтезу цього білка клітинами децидуальної оболонки після настання вагітності, а також із превалюванням INF-γ і TNF-α на ранніх термінах вагітності у жінок з ХЕ в анамнезі. Це створює умови для порушення імунологічної толерантності між маткою та плодом і є однією з провідних причин виникнення самовільного викидня у жінок, що завагітніли на фоні нелікованого ХЕ. Проведення преконцепційного лікування ХЕ запобігає формуванню цитокінового дисбалансу і підвищує синтез глікоделіну на ранніх термінах гестації, що протектує перебіг вагітності і зменшує частоту її переривання в ранніх термінах в 4,6 разів.

Ключові слова: хронічний ендометрит; самовільний викидень; гліколелін, INF-γ; TNF-α.

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

Contact information:
Volodimir Likhachov – Doctor of Medical Sciences, Full Professor, Head of the Department of Obstetrics and Gynecology № 2, Poltava State Medical University (Poltava, Ukraine)
ORCID ID: https://orcid.org/0000-0003-4823-2X
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57205560361
Researcher ID: https://www.reseachrid.com/rid/ABD-4253-2020

Olena Taranovska – Candidate of Medical Sciences, Docent, Associate Professor of the Department of Obstetrics and Gynecology № 2, Poltava State Medical University (Poltava, Ukraine)
e-mail: elenagudyma31@gmail.com
ORCID ID: https://orcid.org/0000-0003-3409-7130
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57206904238
Researcher ID: https://www.reseachrid.com/rid/ABD-4306-2020

Iryna Zhabchenko – doctor of medicine, professor, head of the scientific department of the State University «Institute of Pediatrics, Obstetrics and Gynecology named after Academician O. M. Lukyanova National Academy of Sciences of Ukraine» (Kyiv, Ukraine)
ORCID ID: https://orcid.org/0000-0001-5622-5813
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57208341683

Valeriy Oksyuta – Doctor of Medicine, Associate Professor of the Department of Medical and Preventive Disciplines and Laboratory Diagnostics of the Communal Institution of Higher Education «Rivne Medical Academy» of the Rivne Regional Council (Rivne, Ukraine)
e-mail: voxuta@rma.edu.ua
ORCID ID: https://orcid.org/0000-0002-7831-6860

Vasyl Palapa – Doctor of Medicine, Head of the Department of Medical and Preventive Disciplines and Laboratory Diagnostics of the Communal Institution of Higher Education «Rivne Medical Academy» of the Rivne Regional Council (Rivne, Ukraine)
e-mail: palapa.v.v@rma.edu.ua
ORCID ID: https://orcid.org/0000-0003-3076-9817

Ella Krutikova – Doctor of Medicine, Associate Professor of the Department of Obstetrics and Gynecology No. 1 of the Poltava State Medical University (Poltava, Ukraine)
e-mail: e.krutikova@pdmu.edu.ua
ORCID ID: https://orcid.org/0000-0002-9403-3000
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=6505957783
Researcher ID: http://surl.li/syhfd KIB-9721-2024

Контактна інформація:
Ліхачов Володимир Костянтинович – д.мед.н., професор, завідувач кафедри акушерства та гінекології № 1 Полтавського державного медичного університету (м. Полтава, Україна)
e-mail: v.likhachov@pdmu.edu.ua
ORCID ID: https://orcid.org/0000-0003-4823-2X
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57205560361
Researcher ID: https://www.reseachrid.com/rid/ABD-4253-2020

Тарановська Олена Олексіївна – к.мед.н., доцент, доцент закладу вищої освіти кафедри акушерства та гінекології № 1 Полтавського державного медичного університету (м. Полтава, Україна)
e-mail: elenagudyma31@gmail.com
ORCID ID: https://orcid.org/0000-0003-3409-7130
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57206904238
Researcher ID: https://www.reseachrid.com/rid/ABD-4306-2020

Жабченко Ірина Анатоліївна – д.мед.н., професор, завідувачка науковим відділенням ДУ «Інститут педіатрії, акушерства та гінекології імені академіка О. М. Лук'янової НАМН України» (м. Київ, Україна)
ORCID ID: https://orcid.org/0000-0001-5622-5813
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=57208341683

Оксюта Валерій Миколайович – к.мед.н., доцент кафедри медико-профілактичних дисциплін та лабораторної діагностики Комунального закладу вищої освіти «Рівненська медична академія» Рівненської обласної ради (м. Рівне, Україна)
e-mail: voxuta@rma.edu.ua
ORCID ID: https://orcid.org/0000-0002-7831-6860

Палапа Василь Васильович – к.мед.н., завідувач кафедри медико-профілактичних дисциплін та лабораторної діагностики Комунального закладу вищої освіти «Рівненська медична академія» Рівненської обласної ради (м. Рівне, Україна)
e-mail: palapa.v.v@rma.edu.ua
ORCID ID: https://orcid.org/0000-0003-3076-9817

Крутікова Елла Іванівна – к.мед.н., доцент кафедри акушерства і гінекології № 1 Полтавського державного медичного університету (м. Полтава, Україна)
e-mail: e.krutikova@pdmu.edu.ua
ORCID ID: https://orcid.org/0000-0002-9403-3000
Scopus Author ID: https://www.scopus.com/detail.uri?authorId=6505957783
Researcher ID: http://surl.li/syhfd KIB-9721-2024

Received for editorial office on 10/02/2024
Signed for printing on 10/04/2024