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The Level of Pro-And Anti-Inflammatory Cytokines in Pregnant Women with a History of Cesarean Section

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Abstract: The results of a follow-up study of 53 pregnant women at 38-40 weeks gestation who were scheduled for cesarean section are presented. The aim of the study was to compare the levels of pro-(IL-1b, IL-6) and anti-inflammatory (IL-10) cytokines in pregnant women delivered by cesarean section. The content of pro - and anti-inflammatory cytokines (IL-1b, IL-6, IL-10) was determined. in blood plasma and endometrium collected immediately after fetal extraction.

Keywords: pregnancy, cesarean section, uterine scar, inflammation, immunity, cytokines.

I. Introduction

An increase in the frequency of surgical delivery by caesarean section (CS) has led to an increase in pregnant women with uterine scarring. Usually, the prognosis in the obstetric and gynecological plan for patients who have undergone CS is unfavorable. Over the past 10 years, the frequency of cesarean sections in Uzbekistan has increased to 23%, and in obstetric hospitals and large perinatal centers it reaches 32% or more [1]. There is a constant increase in the incidence of newborns born to mothers with a burdened obstetric-gynecological and somatic anamnesis and gestational complications [6]. The absence of a pronounced trend towards a decrease in perinatal mortality, as well as the increasing infant morbidity, convince us that this operation cannot be a universal means of rational delivery [7, 17,17].

The development of scar failure after cesarean section (CS) on the background of endometritis and gynecological diseases, develops due to the formation of extensive granulation zones with the outcome in the fibrous tissue with prolonged granulomatous inflammation [13]. In the etiology of the formation of an in coherent uterine scar, the erased form of postpartum endometritis also has an erased form, which is manifested by an acute phase, poor clinical

symptoms [14]. Recent studies show that the course of pregnancy with a scar on the uterus cannot be attributed to physiological. It is characterized by the threat of interruption, abnormalities in the placenta's location and attachment, and placenta ingrowth into the scar, which create unfavorable conditions for the development of fetoplacental complex disorders and fetal health [4,15,16]. The development of placental insufficiency, fetal developmental delay syndrome, etc., is usually associated with a violation of immune relationships in the mother-placenta-fetus system [20].

It should be noted that the natural decrease in women's immunity as a result of surgery can cause the development of postpartum septic diseases. An increase in the frequency of operative delivery leads to maternal morbidity, which increases 3-4 times during preventive repeated cesarean section than during natural delivery [8,9,10]. The frequency of intraoperative and postoperative complications during repeated cesarean section varies from 2 to 20.5%, and is higher than during the first CS [6,14]. The rate of delivery through the natural birth canal in women with scarring ranges from 15% to 30-80% [4,7,11].

It has now become apparent that the protection of the fetus from a damaging maternal immune response is based on a complex mechanism and that communication between different steps in the cascade of events is carried out by cytokines. A certain ratio of IL-2, IFN, IL-4, and IL-6, as well as the balance of their synthesis by different cell pools, is important for the physiological course of pregnancy. According to various authors, in the early stages of uncomplicated pregnancy, the pool of IL-4^+ Th2 and IL-10 prevails in the peripheral blood of the mother. Consequently, cytokines have an immunedystrophic, immunosuppressive, and immunotrophic effect [14,15,16,17, 20].

Cytokines produced by endometrial, myometrial and trophoblast cells and their receptors contribute to the successful course of pregnancy. These data indicate a diverse and active involvement of cytokines in reproductive processes at all stages of pregnancy [18, 19,]. Special attention should be paid to the state of the cytokine profile in women with physiological pregnancy, delivered by caesarean section. One of the main functions of the immune system is to control reproduction at both the systemic and local levels. A large number of immune functions are mediated by soluble factors, among which pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, TNFα are isolated, and anti-inflammatory cytokines such as TGFβ and IL-1RRA, which have a pronounced distant effect. They practically do not enter the bloodstream and do not have systemic effects, but under the influence of various endogenous and exogenous factors, an increase in their concentration in peripheral blood can be observed, which indicates a violation of the principle of local functioning of the cytokine network.

II. AIm of the work

The aim of this study was to compare the levels of pro-inflammatory (IL-1b, IL-6) and anti-inflammatory (IL-10) cytokinesов y in pregnant women delivered by elective caesarean section.

III. Materials and methods

The study included 53pregnant women at 38-40 weeks of gestation, aged2-0-37years, who were in the hospital department and Termez City Medical Association, who were recommended for elective caesarean section, who signed an informed consent to participate in the study. Pregnant women were divided into groups: group 1 consisted of 20 women with repeated labor and 1 uterine scar after the previous cesarean section, group 2 consisted of 15 women with uterine scars after the previous 2 or more cesarean sections, and the control group consisted of 18 pregnant women who were scheduled for the first C-section. a caesarean section.

The levels of pro-and anti-inflammatory cytokines (IL-1b, IL-6, and IL-10) were studied. The material for the study was blood plasma and endometrium collected immediately after fetal extraction. The study was conducted by the method of enzyme-linked immunosorbent assay (ELISA) using kits from the Vector Best company (Russia).

Statistical processing was performed using the program "Statistics 6", using statistical methods based on Student criteria. The differences were considered statistically significant at P<0.05. Descriptive statistics displayed quantitative information: the mean value (M) and the standard error of the mean (m).

IV. Results

Analysis of the anamnestic data of the examined women showed that y 64.15% had chronic infectious and inflammatory diseases, such as pelvic inflammatory diseases, urogenital infections, gestational hypertension, anemia of the first and second degrees. In almost all the women examined, the course of pregnancy was complicated: in 67% - hypertensive disorders against the background of cardiac pathology, in 54% - the threat of termination of pregnancy. Ultrasound examination revealed polyhydramnios (10%), thickening and premature maturation of the placenta (12%), which are signs of (intrauterine infection of the fetus.

When studying the level of serum cytokines, it was found that in pregnant women of the control group with a gestation period of 38-40 weeks , the level of IL-1β averaged 218.4 ± 10.9,9 pg/ml, but in women with a uterine scar, group 1, the level of IL-1 β was significantly higher than in women with a scar on the uterus. pregnant women of the control group (P<0.01), averaging 257.9 ± 11.1 pg/ml, which indicates the presence of those inflammatory reactions in which the inducible cytokine reacts first. Analyzing the results of a study on the level of IL-1β in women with repeated scarring on the uterus, its increased content was found not only in relation to the control group (P<0.001), but also to the data of women with one uterine scar (P<0.05), averaging 323.7 ± 12.5 pg/ ml. IL-1b is one of the key mediators of the inflammatory response and plays an important role at all stages of pregnancy. High cytokine activity at this stage, in terms of 38-40 weeks of gestation, is associated with an increase in the need for placental metabolism and preparation of the body for the final stage of gestation. Its main function is to activate the immune system, stimulate angiogenesis, and remodel tissues. However, excessive production of IL-1b can contribute to the development of pathological processes, including pregnancy complications at any gestational stage. (table 1).

Table 1. Cytokine level in pregnant women of the control group, pg/ ml

Cytokines,	Cont. gr., n=18	Group 1, n=20	Group 2, n=15
IL-1β, pg/ ml	218,4 ± 10,9	257,9± 11,1*	323,7 ± 12,5* **
IL-6, pg/ ml	88.6 ± 5.1	91,3 ± 5,2*	138,6 ± 6,8* **
IL-10, pg/ ml	27,3 ± 1,8	35,6 ± 2,1*	41,2 ± 2,3* **

Note:*The values are reliable in relation to the data of the control group; * * The values are reliable in relation to the data of the 1st group. (P<0,05 – 0,001)

IL-6 is a universal cytokine involved in the regulation of both inflammatory and regenerative processes. It stimulates the cellular immune response by activating macrophages, neutrophils, and other effector cells. In our studies, the level of IL-6 in women of the control group averaged 88.6±5.1 pg/ml, but the value of this cytokine in women with a uterine scar was higher than the values of the control group - 91.3 ± 5.2 pg/ml (P<0.05). It should be noted that the maximum level of IL-6 was recorded in women with 2 or 3 uterine scars and averaged 138.6±6.8 pg/ml, which is 1.56 times higher than the values of the control group (P<0.01). There was also a significant difference in comparison with the data of the 1st group (P<0.05).

An important step in our study was to study the level oforo anti-inflammatory cytokinea-IL-10, which playsea central role in maintaining immunological tolerance during pregnancy. The level of IL-10 in women of the control group was 27.3 ± 1.8 pg/ ml. As can be seen from the data

presented in Table 1, the level of IL-10 in women with a uterine scar is significantly higher than in women in the control group (P<0.05) and even higher in women with multiple scars (P<0.01).

The next stage of our research was to study the level of cytokines in the blood serum immediately after cesarean section and the endometrium taken immediately after fetal extraction.

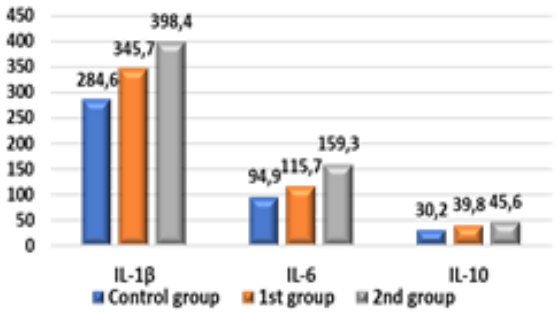

Figure 1. Serum cytokine levels in women after cesarean section, pg/ ml

As can be seen from the data presented in Figure 1, the level of all studied cytokines is higher than at the end of pregnancy. This is the body's natural immunological response to surgery. However, it should be noted that the values of the studied cytokines in women with a uterine scar, and especially with a large number of uterine scars, are higher than those of women who underwent the first cesarean section.

At the moment, a large amount of data is presented indicating the important role of cytokines in reproduction: endometrial development, embryo implantation, and trophoblast growth. Cytokines produced by endometrial, myometrial and trophoblast cells and their receptors contribute to the successful course of pregnancy, but an increased level of cytokines indicates the presence of inflammatory processes that lead to various complications. These data indicate a diverse and active participation of cytokines in reproductive processes at all stages of pregnancy, both in normal and in various deviations from the norm.

Table 2 contains data on cytokine levels in endometrial tissue in women who have undergone cesarean section, with a different number of uterine scars. Three groups of women are considered: those who have had their first C-section, those who have already had one uterine scar after a previous C-section, and those who have two or three scars. As can be seen from Table 2, the level of IL-1b increases with an increase in the number of scars: in women after the first cesarean section, it was and on average 672.4 ± 23.8 pg/ ml, but its level increases with an increase in the number of scars: in women with one scar, the level of IL-1β averaged 795.3±27.6 pg/ ml, which is significantly higher than in women who had their first caesarean section (P<0.05). And in women with two or three scars, the level of this cytokine was even higher – 829.6±29.4 pg/ ml (P<0.01).

Table 2. The level of cytokines in the endometrial tissue in the examined women, M±m

Cytokines,	Cont. gr., n=18	Group 1, n=20	Group 2, n=15
IL-1β, pg/ ml	672,4 ± 23,8	795,3 ± 27,6*	829,6 ± 29,4* **
IL-6, pg/ ml	35.4 ± 2.3	42.7± 2.6*	43.5 ± 2.7*
IL-10, pg/ ml	26.7 ± 1.6	30.2 ± 2.2	29.8 ± 1.9

Note: *The values are valid in relation to the data of the control group; * * The values are valid in relation to the data of the 1st group. (P<0,05 – 0,001)

Analysis of IL-6 data showed a similary trend: 35.4±2.3 pg/ ml after the first cesarean section, 42.7±2.6 pg/ ml in the presence of one scar, and 43.5±2.7 pg/ ml in women with two or three scars (P<0.05).

The results of the study on the level of IL-10 showed that its level varies, but in general there is also an increasing trend: 26.7±1.6 pg/ ml in first-time mothers with cesarean section, 30.2±2.4 pg / ml in women with one scar, 29.8±1.9 pg/ml in women with two or three scarring.

Conclusion.

Thus, with an increase in the number of uterine scars, the level of inflammatory cytokines (IL-1b and IL-6) increases, which may indicate the presence of a chronic inflammatory process or changes in the reparative mechanisms in the endometrium.

The data obtained suggest that repeated cesarean sections and, as a result, an increase in the number of uterine scars have a significant effect on the endometrial immune homeostasis. Elevated levels of IL-1b and IL-6, key pro-inflammatory cytokines, may indicate persistent inflammation, which, in turn, can negatively affect tissue repair processes and endometrial function.

Despite the fact that the level of IL-10, a cytokine with an anti-inflammatory effect, also shows an increasing trend, its dynamics may not be sufficient to compensate for the increased inflammatory response caused by repeated surgical interventions.

Further research is needed to better understand the mechanisms of the impact of uterine scarring on endometrial health and to develop strategies for the prevention and treatment of possible complications associated with chronic inflammation in this area. Special attention should be paid to studying the interaction of various cytokines and their role in the processes of tissue regeneration after cesarean section.

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