

THE CYTOKINE SYSTEM IN THE SECOND HALF OF PHYSIOLOGICAL PREGNANCY AND DURING LABOR

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Abstract

A study was conducted to study the level of anti-inflammatory (IL-4) and pro-inflammatory (IL-1 β , IL-6, IFN γ , TNF α) cytokines in 28 women with physiological pregnancy in the third trimester and in 23 women with incipient labor. It was found that in the prenatal period, the level of IL-1 β and IL-8 increases sharply, and the level of IL-4 decreases sharply. The levels of IL-6 and TNF α are also slightly elevated. Therefore, the study of the level of pro- and anti-inflammatory cytokines in parturient women with a physiologically proceeding pregnancy is of great interest, since it is this mechanism of changes in the level of cytokines during incipient labor activity that is observed in a pathologically proceeding pregnancy with the threat of premature birth.

Keywords: physiological pregnancy, women in labor, cytokines.

Introduction

As is known, the nature of immunological interactions between mother and child in the prenatal period largely determines the physiological and pathological course of pregnancy and childbirth [1,2,3,4,5,6,7,8,9,10].

A special role is assigned to mediators, i.e. cytokines, the immune system in the regulation of the immune response. Cytokines are traditionally the subject of special attention from researchers involved in the problems of reproductive immunology, which is associated with the participation of cytokines in the implementation of almost all stages of the gestational process. They regulate the implantation of the blastocyst, the growth of the placenta and fetus, the production of placental hormones and specific proteins, cell apoptosis, the supervision of the microflora of the reproductive tract, preparation for childbirth and the unleashing of labor [11,12,13,14,15,16,17,18,19,20]. Moreover, during pregnancy, the significance of certain factors changes, which is due to the peculiarities of the stages of placenta formation and changes in the population composition of cytokine-producing cells in the dynamics of the gestational process [21,22,23,24,25].

It is of great interest to study the level of pro- and anti-inflammatory cytokines in women in labor with a physiological pregnancy, since it is this mechanism of changing the level of cytokines during incipient labor activity that is observed in pathologically proceeding pregnancy with the threat of premature birth [26,27,28,29,30,31].

The study of the level of cytokines that regulate the gestational period provides information on the functional activity of cells, the stage of the inflammatory process and its severity, the ratio of activation processes of cytokine-producing T-lymphocytes, which is of great diagnostic and prognostic value [32,33,34,35,36,37,38,39,40].

In order to understand the change in the content of cytokines in the pathology of pregnancy, we analyzed the synthesis of pro- and anti-inflammatory cytokines in healthy pregnant women at 37-42 weeks of gestation and in parturient women. The smooth muscle of the uterus remains stable throughout pregnancy, allowing the fetus to develop in a constant environment. During childbirth, there is a synchronous contraction of the uterine myometrium, combined with short periods of relaxation. The initiation of contractions of the myometrium requires its transformation from a state of rest to activation. This is facilitated by a change in the local concentration of some factors and their receptors [41,42,43,44,45]. Potential stimulators of contractile activity of the myometrium are prostaglandins E₂ and F₂α. They are regarded as the main factors in the initiation of childbirth. The biosynthesis and metabolism of prostaglandins in gestational tissues is directly regulated by cytokines [46,47,48,49,50,51].

The concentration of prostaglandins can also be regulated as a result of changes in the level of inactivators of their metabolism. The enzyme that catabolizes prostaglandins, 15-hydroxyprostaglandin dehydrogenase (PDGH), is abundant in the chorion, placental trophoblast, and decidua [15,16,17,18,19,20]. It is possible that this enzyme inhibits the action of amniotic fluid prostaglandins on the contractile activity of the myometrium. The expression and activity of PDGH in gestational membranes and trophoblast cultures is reduced by exposure to IL-1β and TNFα. The level of PDGH due to the expression of IL-1β and TNFα in the lower segments of the uterus and in the trophoblast decreases during childbirth, which, in turn, can lead to activation of the myometrium [21,22,23,24,25].

A powerful agent of myometrial constriction is platelet-activating factor (PAF) produced by neutrophils. It is already known that PAF slows down the time of onset of labor [1,2,3,4,5,6]. It is assumed that an important role in the initiation of labor can be played by a decrease in production of the soluble TNFR1 receptor in the syncytiotrophoblast before delivery [7,8,9,10]. A high level of this receptor throughout the gestational process can effectively block high doses of TNFα, and a decrease in the level of TNFR1 before delivery seems to promote the accumulation of free TNFα and thus stimulate the synthesis of prostaglandin F₂α, leading to the initiation of uterine contraction [11,12,13,14]. Many authors are of the opinion that timely delivery is associated with inhibition or complete suppression of the production of anti-inflammatory factors, which leads to the development of inflammatory reactions necessary for a successful delivery [51,52,53,54,55].

The aim of the study was to study pro- and anti-inflammatory cytokines in women in the third trimester of pregnancy and in women with incipient labor.

Materials and research methods

We examined 28 women with a physiological pregnancy in the third trimester, who were registered with the consultative polyclinic and 23 women with incipient labor, who were in the maternity complex №3 in Tashkent with a period of 37-41 weeks of gestation. The age of the examined patients ranged from 22 to 34 years. All examined women were practically healthy without somatic and obstetric pathologies. All women underwent complex prenatal diagnostics using instrumental research methods (ultrasound, Doppler), laboratory tests (general blood analysis and urine). Immunological studies were carried out by studying the level of cytokines (IL-1β, IL-4, IL-6, IL-8, IFNγ, TNFα) in blood serum by ELISA according to the attached instructions. The test systems of Vector Best LLC (RF) were used.

Statistical processing of the obtained results was carried out using the Student's t-test using the standard Windows 2000 statistical software package.

Results of the study and their discussion

An analysis of the anamnestic data showed that the examined women were aged 22 to 37 years with an average value of 28,5±2,3 years. The mean duration of pregnancy was 39,9 ± 1,05 weeks. In total, 28 (54,9%) of the examined women were primiparous, 23 (45,1%) were multiparous. 18 (35,3%) women had a history of

gynecological diseases, 22 (43,2%) women performed medical abortions. Extragenital diseases were detected in 24 (47,05%). 12 (23,5%) women had cardiovascular diseases. Pathology of the thyroid gland, occurring in the form of diffuse goiter of I and II degrees, was detected in 21 (41,2%) women. Complications of the first half of pregnancy were noted in 18 (33,3%) women. Among the examined women, the first half of pregnancy was complicated by early toxicosis in 15 (29,4%) women. The frequency of threatened miscarriage was 17,6% (9). Complications of the second half of pregnancy had 8 (15,6%) women.

Analysis of the results of the study on the study of the level of cytokines showed that the concentration of the pro-inflammatory cytokine - IL-1 β in the blood serum of women in the first stage of labor was significantly increased compared with the data of women in the III trimester of pregnancy (P<0.01) (Table 1). So, if in the III trimester of pregnancy the level of IL-1 β averaged 188.6 \pm 17.3 pg/ml, then in parturient women this indicator was increased by 1,5 times and averaged 283,2 \pm 14,1 pg / ml. ml, (P<0.01). Together with other pro-inflammatory factors (platelet activating factor, IL-6, IL-8, prostaglandins E2 and F2 α) IL-1 β is involved in the initiation of labor.

Table 1. The level of cytokines in women of the control group at 37-42 weeks of gestation during labor, M \pm m

Immunological Indicators	III trimester physiological/grav.,n=28	Labor n=23	P
IL-1 β , pg/ml	188,6 \pm 17,3	283,2 \pm 14,1	P<0,01
IL-4, pg/ml	148,5 \pm 15,4	33,8 \pm 2,4	P<0,001
IL-6, pg/ml	56,9 \pm 2,8	89,5 \pm 5,9	P<0,01
IL-8, pg/ml	20,8 \pm 1,6	226,4 \pm 17,3	P<0,001
INF γ , pg/ml	28,3 \pm 1,4	32,8 \pm 2,7	P<0,05
TNF α , pg/ml	48,3 \pm 3,4	56,8 \pm 2,9	P<0,05

The results of the study showed that the concentration of IL-4 in women in the III trimester of pregnancy averaged 148,5 \pm 15,4 pg / ml, and in parturient women, the level of anti-inflammatory cytokine decreased by almost 4 times and averaged 33,8 \pm 2,4 pg/ml, (P<0,001).

This fact seems to be due to the fact that IL-4 reduces the production of prostaglandins by decidual cells, causing an increase in the synthesis of IL-1RA.

As can be seen from Table 1, the development of labor activity is characterized by a significant increase in the level of IL-6 -89,5 \pm 5,9 pg / ml against the values of the group of pregnant women of the last trimester of pregnancy 56,9 \pm 2,8 pg / ml, P<0,01. This dependence is associated with the effect of IL-6 on the level of endothelin. Endothelin is also a potential activator of myometrial contractile activity.

Less studied is the issue of systemic production of chemokines during childbirth. According to our data, there is a multiple increase in the expression of IL-8, almost 11 times, p<0,001. This fact, apparently, indicates the involvement of IL-8 in the remodeling of connective tissues, which takes place during the maturation of the cervix immediately before the onset of labor. This hypothesis is supported by data on increased expression of IL-8 receptors in the tissues of the placenta and myometrium immediately after the initiation of labor. In the experiment, it was found that intracervical administration of IL-8 for 2 days stimulated the process of maturation of the cervix. Using electron microscopy, it was shown that under these conditions, dissolution of collagen fibers, stromal edema, and infiltration by polymorphonuclear leukocytes were observed in the cervix. The accumulation of neutrophils in the connective tissue, in turn, led to a decrease in the concentration of collagen in the cervix, an increase in the level of water in the tissue, which ultimately determined the maturation of the cervix.

The content of $\text{INF}\gamma$ during the development of labor underwent minor changes compared to the change in the production of other cytokines, while its increase to $32,8 \pm 2,7$ pg/ml was noted against the values of the third trimester $28,3 \pm 1,4$ pg/ml, $p < 0,05$. Probably, the content of this cytokine is determined not only by the secretory function of cells of the immune system, but also by the activity of other cell types, for example, syncytiotrophoblast and decidual cells.

$\text{TNF}\alpha$ is one of the most pleiotropic cytokines that affects all cells, changing their growth, differentiation and survival. In women in the third trimester of pregnancy, the level of $\text{TNF}\alpha$ averaged $50,2 \pm 3,4$ pg/ml; in parturients, the level of this cytokine remained almost unchanged and averaged $52,8 \pm 2,9$ pg/ml, which was consistent.

Due to the fact that mainly two parameters, IL-4 and IL-8, undergo a sharp change during labor, we considered it appropriate to calculate an index that combines these indicators using the following formula: $\text{FRI} = \text{IL-8}/\text{IL-4}$ where FRI is the fetal rejection index.

With physiologically proceeding labor activity, this index is 6,7. And in the third trimester of pregnancy, this ratio is 0,14. This means that the body is not ready to reject the fetus, i.e. the gestational period continues and the level of factors causing the development of contractile activity of the uterine myometrium is reduced.

Thus, by the time of delivery, there is an increase in the level of pro-inflammatory cytokines, against the background of a decrease in the production of anti-inflammatory cytokines, which, apparently, is a powerful factor in the regulation of the production of prostaglandins that determine the development of contractile activity of the uterine myometrium during childbirth.

Conclusions

In pregnant women in the third trimester, the level of anti-inflammatory cytokine IL-4 and pro-inflammatory cytokine IL- β is increased. With the onset of labor activity, there is a sharp decrease in the anti-inflammatory cytokine - IL-4 and an increase in IL-8.

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