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The State of the Cytokine Status in Pregnant Women with Fetal Growth Retardation

Mavlyanova N.N[1*], Ixtiyarova G.I[2], Tosheva I.I[2], Aslonova M.Zh[2] and Narzullaeva N.S[2]

[1]*Republican Specialized Scientific and Practical Medical Center of Obstetrics and Gynecology under the Ministry of Health of the Republic of Uzbekistan.*

[2]*Department of Obstetrics and Gynecology, Bukhara State Medical Institute. Abu Ali Ibn Sina of the Ministry of Health of Uzbekistan.*

[*]Correspondence:
Mavlyanova N.N, Republican Specialized Scientific and Practical Medical Center of Obstetrics and Gynecology under the Ministry of Health of the Republic of Uzbekistan.

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ABSTRACT

The article provides a study of cytokine status in fetal growth retardation. The study reveals that pregnant women with severe fetal growth retardation have an increased concentration of pro- (IL-6, FNO-alfa, INF-g) and anti-inflammatory cytokines (IL-4 and IL-6), along with an increase in cytotoxic reactions in the placenta, development of systemic endothelial dysfunction with an autoimmune process, which cause angiogenesis disorders.

Keywords

Fetal growth restriction syndrome, Fetoplacental insufficiency, cytokines (FNO-alfa, INF-gamma, IL-4 and IL-6, IL-10).

Introduction

According to numerous studies, in most cases, the favorable course of pregnancy depends on the immunological control of the relationship between the mother and the fetus. One of the most important tasks of modern obstetrics is to reduce reproductive losses which refer to fetal loss throughout the gestation period, as well as the death of children in early neonatal age [1,3,4,5,8,10,14,15,22]. It should be mentioned that placental insufficiency (PI) accounts to more than 35% of causes of perinatal and infant mortality [6,7,8,16,18.20].

The main clinical manifestations of PI are chronic intrauterine hypoxia and fetal growth retardation (FGR) - intrauterine growth retardation. It is intrauterine hypoxia and FGR that can cause abortion and fetal death, as well as the occurrence of somatic, mental and reproductive pathologies in further periods of individual development [19].

So far, the mechanisms for the immunological control of trophoblast invasion into the uterine wall have already been studied, as well as the mechanisms for the formation of immunological tolerance in the mother - fetus system. However, there is still no consensus on the nature of changes in the placental cytokine network in the physiological pregnancy and obstetric pathology, especially in fetal growth retardation [10].

An integrated approach to the study of immunological regulatory mechanisms, the role of cellular factors in controlling both normal and pathological placenta development shall contribute to the disclosure of immunopathogenesis in fetal growth retardation.

The study aimed to assess the status of pro- and anti-inflammatory cytokines in the clinical course of fetal growth retardation.

Materials and Methods

We examined 103 pregnant women aged 19 to 45 years. All the women have been kept under observation at the clinic of the State institution, Republican specialized scientific and practical medical center obstetrics and gynecology under the Ministry of Health of the Republic of Uzbekistan. All pregnant women underwent general clinical, functional, and immunological ELISA studies. All pregnant women consulted with other specialists - a neurologist, therapist, cardiologist, hematologist, a specialist in communicable diseases, etc.

Serum cytokines levels were measured via enzyme-linked immunosorbent assay (ELISA). To measure the levels of cytokines FNO-alfa, INF-gamma, IL-4 and IL-6, IL-10, we used the test systems developed at ZAO Vector-Best (Novosibirsk).

These test systems are based on the sandwich method of solid-phase ELISA using horseradish peroxidase as an indicator enzyme. After the completion of the main stages of work, 10–15 minutes before the end of the incubation, a solution of the substrate – chromogenic mixture was prepared. Then, the cells of the plate were washed three times by adding 300 µl of washing physiological saline into each of them and 3-5 times with distilled water, followed by its removal by shaking the plate over the sink. Finally, 200 µl of a substrate-chromogenic mixture solution was added to all wells, which was followed by 20-minutes incubation at room temperature in the dark place. The reaction was stopped by adding 50 µl of a solution of sulfuric acid. The results, which express the activity of bound peroxidase, were analyzed via an automatic microtray photometer at a wavelength of 492 nm, with zero absorbance in standertized wells set without detectable cytokine in solution. To perform the quantitative assessment of the results, the calibration curve was drawn manually; the curve reflects the dependence of optical density on standard antigen concentration, and the studied samples can be compared with the curve.

Results

Clinical and laboratory studies of 66 pregnant women with fetal growth retardation contributed to the determibation of severity. So, for example, 39 pregnant women received the diagnosis of FGR-I severity, which amounted to 59.1%, while 24 women (36.6%) had FGR-II severity and 3 pregnant women were diagnosed with FGR-III severity, which amounts to 4.5% of cases.

The study of concomitant pathology in 103 examined pregnant women revealed concomitant somatic disease in 48 of them, which amounts to 46.6%.

The most frequent concominant diagnoses were: blood disorders (anemia) – 40,7% (42), urogenital disorders – 39,8% (41), cardiovascular disorders – 22,3% (23); 5,8% had hepatitis (6) and 4,8% (5) had endocrine systems disorders.

Whereas, in the group of pregnant women with FGR, the most frequently diagnosed diseases were: urogenital disorders - 51.2% (34 out of 66), anemia - 45.5% (30), cardiovascular disease - 34.8% (23), endocrinopathy - 7, 6% (5) and hepatitis - 9.1% (6) cases, respectively. In the group of pregnant women without FGR, 12 out of 37 were diagnosed with anemia (32.4%) and 18.9% (7) women had urogenital disorders.

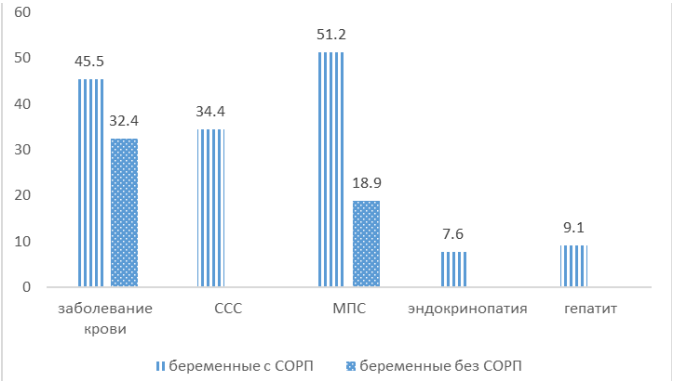

Figure 1: Concominant disorders in pregnant women (with account for FGR), % When analyzing the results of immunological studies, due to a very low amount of the detected cases of FGR-III severity, these pregnant women were included in the group of FGR-II severity (Table 1).

Table 1: Cytokine status indicators in pregnant women with fetal growth retardation (pg/ml).

Group	FNO-alfa	IL4	INF-g	IL-10	IL-6
control group N = 35	5,8 ± 0,9	4,2 ± 0,8	5,5 ± 0,9	10,2 ± 0,9	7,6 ± 0,8
pregnant women without FGR N = 37	15,8 ± 0,3*	5,1 ± 0,04	6,4 ± 0,07	11,03 ± 0,2	17,9 ± 0,5*
pregnant women with FGR N= 66	21,4 ± 0,2* **	7,7 ± 0,1* **	7,8 ± 0,07**	13,2 ± 0,09 **	24,8 ± 0,2* **

Note: * - the measure of reliability in relation to the control group (P <0.05).
** - the measure of reliability in relation to indicators of pregnant women without FGR (P <0,05).

As follows from table, the level of the pro-inflammatory cytokine INF-g averaged 6.4 ± 0.07 pg/ml, which is 1.2 times higher than the control group, but it was not reliable (P> 0.05). The levels of anti-inflammatory cytokines IL-4 and IL-6 also slightly exceeded those of the control individuals, however, they also were unreliable and averaged 5.1 ± 0.04 and 11.03 ± 0.2 pg/ml, respectively (4,2 ± 0,8 and 10,2 ± 0,9 pg/ml in control, P >0,05).

At the same time, the level of proinflammatory cytokines FNO-alfa and IL-6 in the group of pregnant women without FGR averaged 15.8 ± 0.3 pg/ml and pg/ml 17.9 ± 0.5, which is 2.7 and 2, 4 times higher than the control group, respectively (P <0.05). This phenomenon is possibly associated with concomitant pathology of pregnant women without FGR - with the urogenital and blood system (anemia) disorders, which reflects the response of the cellular immune system to bacterial infections in the body.

According to published data, cytokines, germ factors, and chemokines are secreted by various placenta cells throughout pregnancy; they determine the different aspects of the interaction of placenta cells with each other and determine the processes of trophoblast invasion and formation of the vasculature, and inhibit the maternal cytotoxic immune report against fetus [23].

Notably, an increase in the concentration of proinflammatory cytokines FNO-alfa and IL-6 in pregnant women with a physiological course of pregnancy can also be explained by an increase in their anti-apoptotic role in relation to placenta cells and stabilization of proliferative processes in placental tissue, which cause a compensatory reaction in response to an increase in antiangiogenic stimuli in the placental stroma [10].

The study of the state of pro- and anti-inflammatory cytokines in the group of pregnant women with FGR showed a significant increase in their levels compared to the group of pregnant women

with a physiological course of pregnancy. Thus, the concentrations of pro-inflammatory cytokines FNO-alfa, INF-g, and IL-6 were 1.4, 1.2, and 1.4 times higher than in pregnant women without FGR and averaged to 21,4 ± 0,2 pg/ml, 7,8 ± 0,07pg/ml и 24,8 ± 0,2pg/ml, respectively. The results were statistically significant (P <0.05; P <0.001). The level of anti-inflammatory cytokines IL-4 and IL-10 in this group of pregnant women is statistically significantly increased (P <0.05). According to the data published, the data obtained reflect the activation of placental macrophages [25]. An increase in the concentration of IL-6, FNO-alfa, INF-g and anti-inflammatory cytokines IL-4 and IL-10 reflects an imbalance in the cytokine system due to increased activity of placental macrophages and activation of placental endothelial cells.

The data obtained were also analyzed with account of the severity of FGR in pregnant groups (Figure 2).

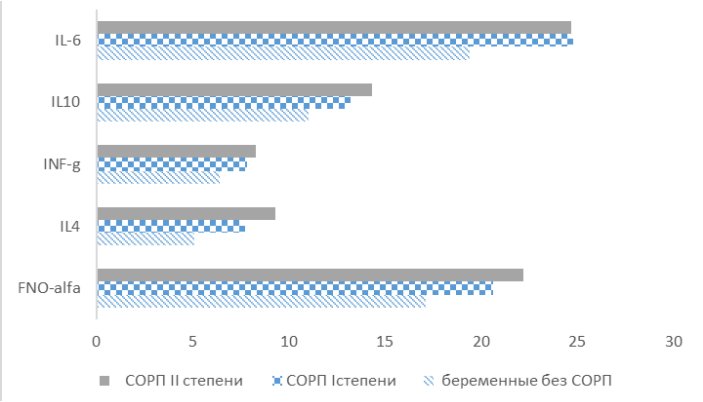

Figure 2: Indicators of cytokine status in pregnant women, with account of the FGR severity (pg/ml) (P <0,05).

As can be seen from Figure 2, the level of FNO-alfa and IL-6 in the group of pregnant women with FGR-I severity was 1.3 and 1.4 times higher than in the group of pregnant women with normal course of pregnancy, this difference is statistically significant (P <0.05). Whereas, in pregnant women with FGR-II severity, the level of FNO-alfa and INF-g was 1.1 and 1.2 times higher than in pregnant women with FGR-I severity and averaged 22.2 ± 0.1 pg/ml and 8.3 ± 0.08 pg/ml, respectively. (P <0.05).

We have estimated the Spearman rank correlation coefficient for cytokine concentrations. This, in the group of pregnant women with FGR-I severity, the level of FNO-alfa had a direct significant positive correlation with the IL-4 indicator - r=+ 0.5 (P <0.05), and IL-6 had an inverse correlation with the anti-inflammatory cytokine IL -4 - r=-0.3 (P <0.05). Such a significance of the cytokine status in pregnant women with FGR-I severity causes acute inflammatory process, which may be due to urogenital disorders, etc.

In women with FGR-II severity, an increased level of INF-g had a direct correlation with FNO-alfa - r = + 0.4 and IL-10 - + r = 0.3 (P <0.05), maintaining active inflammatory process. The anti-inflammatory cytokine IL4 had a significant inverse correlation with IL-10 and IL-6 (r = -0.4, P <0.05), respectively.

Comparison of the obtained results with the published sources reveals that increased levels of pro- (IL-6, FNO-alfa, INF-g) and anti-inflammatory cytokines (IL4 and IL-6) in the body of pregnant women with FGR-II severity characterizes an increase in cytotoxic reactions in the placenta, development of systemic endothelial dysfunction with an autoimmune process, causing disorders in angiogenesis and possibly the formation of mononuclear infiltrates in the placental tissue.

Thus, fetal growth retardation is associated with disorders in interaction between the placental tissue and the mother's immune system, which leads to disorders in the cytokine status in the pregnant body (mother-placenta-fetus) due to an increase in the concentration of pro- (IL-6, FNO-alfa, INF-g) and anti-inflammatory (IL-4. IL-10) cytokines, which is accompanied by the placenta damage, increased death of trophoblast cells and endothelial cells of the placental vessels.

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