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DYNAMICS OF SERUM CYTOKINE AND C-REACTIVE PROTEIN LEVELS DURING PREGNANCY INDUCED IN ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS IN WOMEN OF ADVANCED REPRODUCTIVE AGE

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Summary. Nosenko O. M., Khancha F. O. **DYNAMICS OF SERUM CYTOKINE AND C-REACTIVE PROTEIN LEVELS DURING PREGNANCY INDUCED IN ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS IN WOMEN OF ADVANCED REPRODUCTIVE AGE. -** *[1]Odessa National Medical University; [2]Donetsk National Medical University, Kropivnytskyi; e-mail: office@onmedu.edu.ua;: contact@dsmu.edu.ua.* Gestation is considered an inflammatory process, and a wide range of studies has demonstrated the relevance of analyzing cytokine signatures in both the physiological and pathological course of pregnancy. **The purpose of the study** was to determine the serum levels of pro-inflammatory and anti-inflammatory cytokines and C-reactive protein (CRP) during pregnancy induced in assisted reproductive technology (ART) programs in women of advanced reproductive age. **Material and methods.** 123 women with infertility cured in ART cycles were under observation, including 65 pregnant women of late reproductive age, as well as 58 women of active reproductive age, 57 pregnant women of advanced reproductive age after natural conception. All women's pregnancies ended in childbirth. The average age of examined women of advanced reproductive age with cured infertility in ART programs was 38.71±0.54 years, the group of women of active reproductive age with cured infertility in ART programs was 30.86±0.38 years, the control group of pregnant women of advanced reproductive age after natural conception – 37.65±0.29 years. The levels of pro-inflammatory and anti-inflammatory cytokines were determined by the cytometric method and CRP in blood serum by the immunoturbidimetric method in the dynamics of pregnancy - at 7-8, at 11-12, at 18-20 and at 29-31 weeks. **Results.** It was established that serum levels of interleukin 1β (IL-1β), tumor necrosis factor-α, interferon-γ, IL-2, IL-4, IL-6 and CRP during pregnancy induced during ART in women of advanced reproductive age were statistically significantly different from similar levels during pregnancy induced under during ART in women of active reproductive age and throughout pregnancy after natural conception in women of advanced reproductive age with higher values, while serum IL-10 content was lower. **Conclusion.** Abnormal inflammation and reproductive aging can be a factor in obstetric and perinatal complications of pregnancy induced in ART cycles in women of advanced reproductive age.

Key words: assisted reproductive technologies, induced pregnancy, advanced reproductive age, serum cytokines, C-reactive protein.

Реферат. Носенко О. М., Ханча Ф. О. **ДИНАМІКА РІВНЯ ЦИТОКІНІВ І С-РЕАКТИВНОГО БІЛКА В СИРОВАТЦІ КРОВІ ПІД ЧАС ВАГІТНОСТІ, ІНДУКОВАНОЇ В ПРОГРАМАХ ДОПОМІЖНИХ РЕПРОДУКТИВНИХ ТЕХНОЛОГІЙ У ЖІНОК ПОХИЛОГО РЕПРОДУКТИВНОГО ВІКУ.** Вагітність вважається запальним процесом, і широкий спектр досліджень продемонстрував актуальність аналізу сигнатур цитокінів як у фізіологічному, так і в патологічному перебігу вагітності. Метою дослідження було визначення сироваткових рівнів прозапальних і протизапальних цитокінів і С-реактивного білка (СРБ) під час вагітності, індукованої в програмах допоміжних репродуктивних технологій (ДРТ) у жінок похилого репродуктивного віку. Матеріал і методи. Під спостереженням перебували 123 жінки з безпліддям, вилікуваними в циклах ДРТ, з них 65 вагітних пізнього репродуктивного віку, а також 58 жінок активного репродуктивного віку, 57 вагітних старшого репродуктивного віку після природного зачаття. Вагітність у всіх жінок закінчувалася пологами. Середній вік обстежених жінок похилого репродуктивного віку з вилікуваним безпліддям за програмами ДРТ становив 38,71±0,54 року, група жінок активного репродуктивного віку з вилікуваним безпліддям за програмами ДРТ – 30,86±0,38 року, контрольна група вагітних похилого віку. репродуктивний вік після природного зачаття – 37,65±0,29 років. Рівні прозапальних і протизапальних цитокінів визначали цитометричним методом та СРБ у сироватці крові імунотурбідиметричним методом у динаміці вагітності – на 7-8, 11-12, 18-20 та 29-му роках. 31 тиждень. Результати. Встановлено, що сироваткові рівні інтерлейкіну 1β (IL-1β), фактора некрозу пухлини-α, інтерферону-γ, IL-2, IL-4, IL-6 та СРБ під час вагітності, індукованої під час АРТ у жінок старшого репродуктивного віку, були статистично суттєво відрізнявся від подібних рівнів під час вагітності, індукованих під час АРТ у жінок активного репродуктивного віку, і протягом усієї вагітності після природного зачаття у жінок старшого репродуктивного віку з вищими значеннями, тоді як вміст IL-10 у сироватці був нижчим. Висновок. Аномальне запалення та репродуктивне старіння можуть бути фактором акушерських та перинатальних ускладнень вагітності, спричинених циклами ДРТ у жінок старшого репродуктивного віку.

Ключові слова: допоміжні репродуктивні технології, індукована вагітність, похилий репродуктивний вік, сироваткові цитокіни, С-реактивний білок.

Cytokines are central participants in the modulation of the immune system, and also have a modulatory effect on various tissues and organs. Abnormal changes in the production, ratio, and circulating levels of cytokines are involved in the pathogenesis of organ and system damage [1, 2]. Pregnancy is a complex and dynamic immunological state, and the immune system plays a key role in organizing the stages of normal pregnancy from implantation to delivery. Gestation is considered as an inflammatory process, and a wide range of studies has demonstrated the relevance of analyzing cytokine signatures both during the physiological and pathological course of pregnancy [2, 3].

An acute inflammatory response in pregnant women is not beneficial, as it can affect the health of both the pregnant woman and the fetus. A large number of studies have shown that high levels of C-reactive protein (CRP) and cytokines are associated with pregnancy complications and adverse birth outcomes [4, 5].

Advanced maternal reproductive age (> 35 years) is a risk factor for pregnancy complications, with the incidence of pregnancy at an older age increasing, especially in developed countries, often as a result of treatment in assisted reproductive technology (ART) programs due to reduced fertility. Advanced maternal age is associated with adverse pregnancy outcomes, such as placental dysfunction, fetal growth restriction, perinatal morbidity and stillbirth, preeclampsia, and gestational diabetes [6]. Aging is well known as an age-dependent, chronic, low-grade inflammatory state that occurs due to the accumulation of immune cells and the production of pro-inflammatory cytokines. The profile of molecules secreted by senescent cells has been termed the senescence-associated secretory phenotype (SASP). Various SASPs, including IL-1α, IL-1β, IL-6, and TNFα, clearly show an age-dependent increase in expression, reflecting the novel concept of “inflammation (inflammation + aging)” [7].

The purpose of the study was to determine the levels of pro-inflammatory and anti-inflammatory cytokines and C-reactive protein in blood serum during pregnancy, induced in ART programs, in women of late reproductive age.

Research materials and methods

The study was conducted on the basis of the Department of Obstetrics and Gynecology of the Odesa National Medical University (ONMedU) from 2021 to 2023. It is a fragment of the research topic "Improving methods of prevention, diagnosis and treatment of diseases of the female reproductive system using the latest medical and molecular genetic technologies" (No. State registration 0117U007494), approved by the Commission on Bioethics of ONMedU (Protocol No. 31 dated May 31, 2021), was carried out in compliance with the principles of the Code of Ethics of the World Medical Association (Declaration of Helsinki) regarding research involving human subjects. The clinical bases of the study were Limited Liability Company "Clinic of Reproductive Medicine "Nadia Odesa"" in Odesa, Limited Liability Company "Profile Hospital AIRMED" in Odesa, Communal Non-profit Enterprise "Maternity House No. 7" of Odesa City Council.

123 women with infertility treated in ART cycles were under observation, including 65 pregnant women of advanced reproductive age of group I, 58 women of active reproductive age of group II. Control group K consisted of 57 pregnant women of advanced reproductive age after natural conception. All women's pregnancies ended in childbirth.

All women in the ART group underwent controlled ovarian stimulation in protocols with gonadotropin-releasing hormone antagonists, oocytes were fertilized by intracytoplasmic sperm injection, embryos were vitrified on the 5th day, vitrified/warmed embryos were transferred in a segmented cycle. Pregnancy in the first trimester was supported by estrogen and progesterone preparations, vitamin and mineral complexes.

Peripheral blood samples of 4 ml on an empty stomach were collected from the participants at 7-8, 11-12, 18-20 and 29-31 weeks using EDTA vacutainers. The serum was separated after centrifugation (3,500 rpm) for 10 minutes. during the first 24 h after collection, and the collected plasma was stored in 2-ml aliquots in a freezer with a temperature of -80 °C until determination. The levels of IL-1β, IL-2, IL-4, IL-6, IL-10, interferon-γ (INF-γ) and TNF-α were measured by flow cytometry using the BD Sciences test system on a FACSCalibur analyzer, BD Sciences (USA) according to the manufacturer's instructions. The level of CRP was determined by the immunoturbidimetric method with latex amplification on a Cobas 6000 analyzer (c 501 module) using original test systems from Roche Diagnostics (Switzerland). CRP agglutinate of human origin with latex particles coated with anti-CRP monoclonal antibodies was used. Aggregates were analyzed turbidimetrically.

Statistical processing of the obtained data was carried out using the Excel electronic program with determination of the reliability of differences at a value of $p<0.05$. The average value (M), error of the standard deviation (±SEM) was determined. The Mann-Whitney U-test was used to compare groups based on quantitative characteristics.

Research results and their discussion. The average age of examined women with cured infertility of group I was equal to 38.71±0.54 years ($p_{I-II}<0.01$, $p_{I-k}>0.05$), group II – 30.86±0.38 years ($p_{II-k}<0.01$), group K – 37.65±0.29 years, BMI, respectively, – 24.32±0.58 kg/m^2 ($p_{I-k}>0.05$), 23.47±0.66 kg/m2 ($p_{II-k}>0.05$), 24.27±0.73 kg/m^2.

As the study showed, the levels of serum cytokines such as IL-1β, TNF-α, INF-γ, IL-2, IL-4, IL-6 and CRP during pregnancy induced during ART in women of advanced reproductive age differed from similar levels during pregnancy induced during ART in women of active reproductive age and during pregnancy after natural conception in women of advanced reproductive age with higher values, while serum IL-10 content was lower (table)

IL-1β is an indispensable pro-inflammatory cytokine that promotes the proliferation and maturation of B-cells, NK activation and T-cell stimulation, and is one of the first to be included in the appropriate protective response under the influence of pathogenic factors [8, 9]. IL-1β is a Th1 cytokine, but is also associated with Th17 responses [10]. In the placenta, IL-1β promotes trophoblast differentiation and motility in extravillous trophoblasts of the first trimester [8, 9].

Table – Cytokine profile of peripheral blood serum in the dynamics of pregnancy in women of the studied groups (M±SEM)

Indicator	Pregnancy period, weeks	Group I, n=65	Group II, n=58	Group K, n=65
IL1-β, pg/ml	7-8	10.24±0.15 ^{II,k}	9.21±0.28 ^{I,k}	8,47±0.17
	11-12	12.47±1.68 ^{II,k}	9.36±0.11 ^{I,k}	7.78±0.13
	18-20	15.62±2.34 ^{II,k}	7.22±0.10 ^{I,k}	5.48±0.11
	29-31	17.08±2.63 ^{II,k}	7.38±0.08 ^{I,k}	4.89±0.10
TNF-α,pg/ml	7-8	41.23±1.28 ^{II,k}	24.33±2.18 ^{I,k}	10.38±0.78
	11-12	69.32±2.20 ^{II,k}	35.66±2.65 ^{I,k}	18.34±0.85
	18-20	99.27±3.28 ^{II,k}	44.04±2.49 ^{I,k}	28.46±0.88
	29-31	111.75±3.69 ^{II,k}	48.61±2.60 ^{I,k}	32.49±0.98
INF-γ, pg/ml	7-8	53.63±4.07 ^{II,k}	47.53±4.69 ^{I,k}	32.68±0.44
	11-12	70.64±1.64 ^{II,k}	37.29±2.36 ^{I,k}	28.53±5.17
	18-20	69.17±1.92 ^{II,k}	34.45±2.32 ^{I,k}	19.84±0.84
	29-31	115.34±3.56 ^{II,k}	73.80±5.88 ^{I,k}	33.04±1.14
IL-2, pg/ml	7-8	5.01±0.09 ^{II,k}	2.73±0.29 ^{I,k}	0.71±0.09
	11-12	18.45±0.24 ^{II,k}	8.24±1.03 ^{I,k}	1.12±0.25
	18-20	51.34±1.00 ^{II,k}	10.95±1.20 ^{I,k}	2.75±0.29
	29-31	49.70±1.88 ^{II,k}	17.49±2.12 ^{I,k}	2.40±0.52
IL-4, pg/ml	7-8	32.98±1.97 ^{II,k}	29.01±2.42 ^{I,k}	20.74±0.71
	11-12	71.04±4.15 ^{II,k}	38.17±3.54 ^{I,k}	24.46±0.96
	18-20	85.46±5.06 ^{II,k}	42.25±3.73 ^{I,k}	25.65±1.18
	29-31	86.32±5.20 ^{II,k}	54.28±7.06 ^{I,k}	28.67±1.20
IL-6, pg/ml	7-8	70.01±2.79 ^{II,k}	59.80±5.56 ^{I,k}	53.41±2.65
	11-12	88.81±5.43 ^{II,k}	68.62±5.19 ^{I,k}	62.12±2.57
	18-20	136.20±2.72 ^{II,k}	75.17±6.06 ^{I,k}	70.92±2.05
	29-31	130.09±4.38 ^{II,k}	74.03±1.98 ^{I,k}	66.40±0.76
IL-10, pg/ml	7-8	36.45±0.12 ^{II,k}	40.58±1.11 ^{I,k}	45.69±1.24
	11-12	39.21±1.05 ^{II,k}	48.97±1.35 ^{I,k}	52.17±1.13
	18-20	35.77±1.06 ^{II,k}	47.48±1.52 ^{I,k}	58.12±1.12
	29-31	32.25±0.72 ^{II,k}	45.51±0.74 ^{I,k}	62.52±051
CRP, mg/l	7-8	2.89±0.08 ^{II,k}	2.01±0.14 ^{I,k}	1.62±0.08
	11-12	6.02±0.19 ^{II,k}	4.24±0.29 ^{I,k}	3.29±0.18
	18-20	7.32±0.24 ^{II,k}	5.79±0.40 ^{I,k}	3.72±0.22
	29-31	9.29±0.30 ^{II,k}	7.16±0.50 ^{I,k}	4.87±0.27
Note. $^{I, II, k}$ - a statistically significant difference with the indicators of groups I, II, K ($p<0.05$).				

IL-1β gene polymorphism (-511C/T) can lead to an increase in IL-1β production and the share of NK cells in the lymphocyte population. IL-1β induces the production of TNF-α, and IL-2, IL-6. IL-1β mediates the initiation of preterm labor in the context of infection, and increased levels of IL-1β in the cervix, myometrium, and amniotic membranes in the presence/absence of infection are associated with preterm labor [9]. As can be seen from the table, the expression of IL-1β in the dynamics of the gestational process in all studied groups had a tendency to gradually decrease, but in group I it began to increase in the third trimester. As the research showed, the serum content of IL-1β in women of group I was statistically significantly increased at 7-8 weeks of gestation compared to pregnant women of group II and group K by 1.11 ($p<0.01$) and 1.21 ($p<0.01$) times, at 11-12 weeks – by 1.33 ($p<0.01$) and 1.60 ($p<0.01$) times, respectively, at 18-20 weeks – 2.16 ($p<0.01$) and 2.85 ($p<0.01$) times, 29-31 weeks – 2.32 ($p<0.05$) and 3.49 ($p<0.05$) times (see table, fig. 1).

TNF-α is a potent multipotent cytokine with a very impressive range of effects on a huge variety of cells produced by macrophages. It is one of the most important inflammatory cytokines. TNF-α affects hormone synthesis, placental architecture, embryo development, steroidogenesis,

cyclical processes in the uterus, placental differentiation, and childbirth.

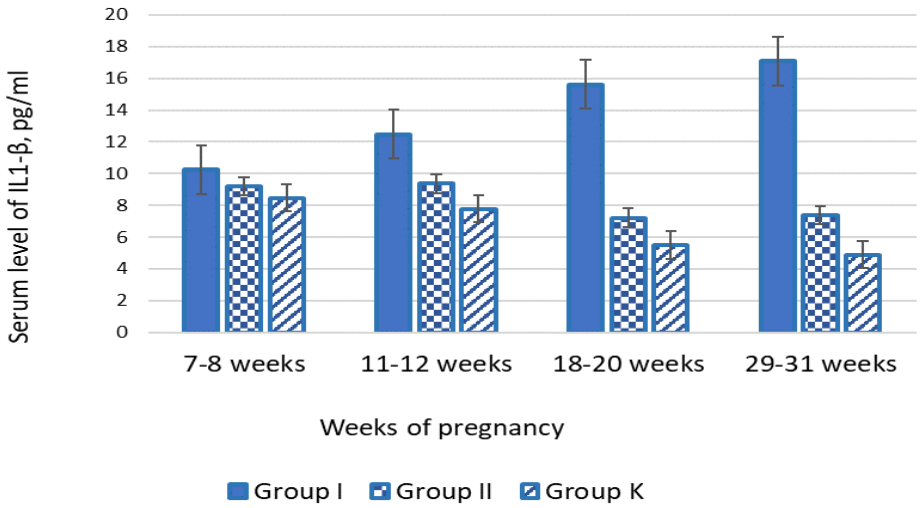

Fig. 1. Serum levels of IL-1β in the dynamics of pregnancy in women of the studied groups

Elevated levels of TNF-α are associated with recurrent miscarriages and infertility [11, 12]. When analyzing the results of the content of TNF-α in the peripheral blood serum of pregnant women of group I, a statistically significant increase in the levels of this cytokine was noted compared to groups II and K: at 7-8 weeks by 1.69 ($p<0.01$) and 3.97 ($p<0.01$) times; at 11-12 weeks – 1.94 ($p<0.01$) and 3.78 ($p<0.01$) times; at 18-20 weeks – 2.25 ($p<0.01$) and 3.49 ($p<0.01$) times; in 29-31 weeks – 2.30 ($p<0.01$) and 3.44 ($p<0.01$) times (see table, fig. 2).

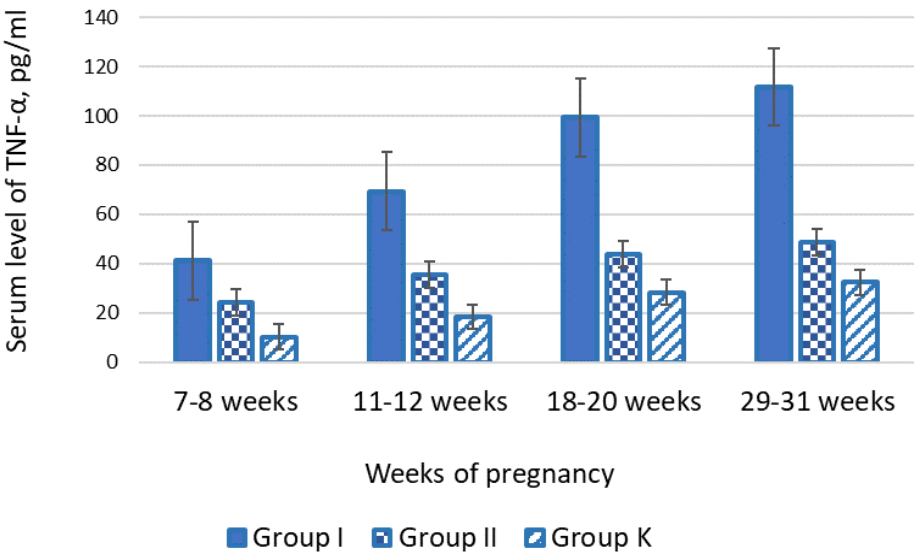

Fig. 2. Serum levels of TNF-α in the dynamics of pregnancy in women of the studied groups

IFN-γ is a pro-inflammatory cytokine released by immune cells, including natural killer and Th1 cells. Both decidual inflammatory cells and the developing embryo release IFN-γ, which supports pregnancy, promotes implantation through vascular remodeling, vascular development at the implantation site, and decidual tissue support during placental development [10]. However, excessive levels of IFN-γ are harmful to the embryo. Most literature sources report a significantly increased expression of IFN-γ in patients with miscarriages or habitual miscarriage [12]. In the

conducted study, the serum content of IFN-γ in women of group I was increased in the gestation period of 7-8 weeks compared to pregnant women of group II and group K, respectively, by 1.13 and 1.64 times; at 11-12 weeks – 1.89 ($p<0.01$) and 2.48 ($p<0.01$) times; at 18-20 weeks – 2.01 ($p<0.01$) and 3.49 ($p<0.01$) times; in 29-31 weeks – 1.56 ($p<0.05$) and 3.49 ($p<0.05$) times (see table, fig. 3).

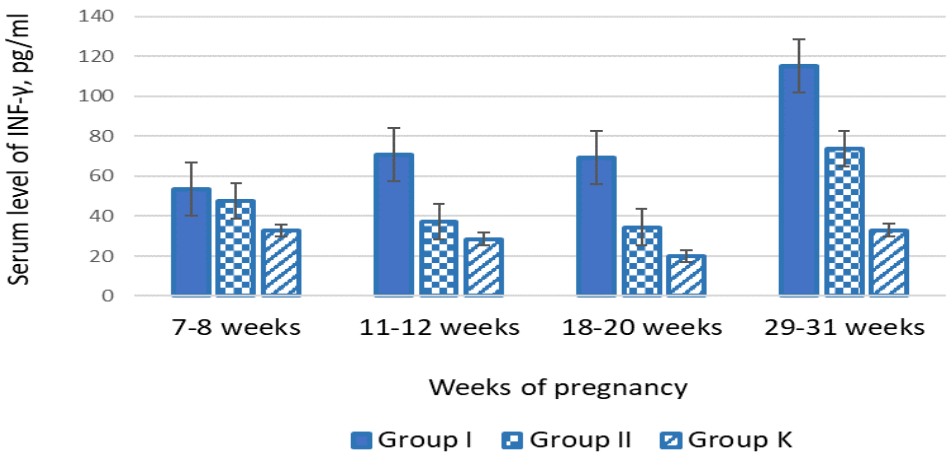

Fig. 3. Serum levels of IFN-γ in the dynamics of pregnancy in women of the studied groups

IL-2 is a proinflammatory cytokine secreted by Th1 cells that proliferates, activates, and mobilizes T cells and natural killer cells [12]. It acts by binding to IL-2R, affecting the differentiation of T lymphocytes into effector and memory T cells, as well as regulatory T cells, which are important in preventing autoimmunity [10]. The serum level of IL-2 in women of group I at the gestation period of 7-8 weeks compared to pregnant women of group II and group K was statistically significantly higher by 1.84 ($p<0.01$) and 7.04 ($p<0.01$) times; at 11-12 weeks – 2.24 ($p<0.01$) and 16.53 ($p<0.01$) times; at 18-20 weeks – 4.69 ($p<0.01$) and 18.67 ($p<0.01$) times; in 29-31 weeks – 2.84 ($p<0.01$) and 20.67 ($p<0.01$) times (see table, fig. 4).

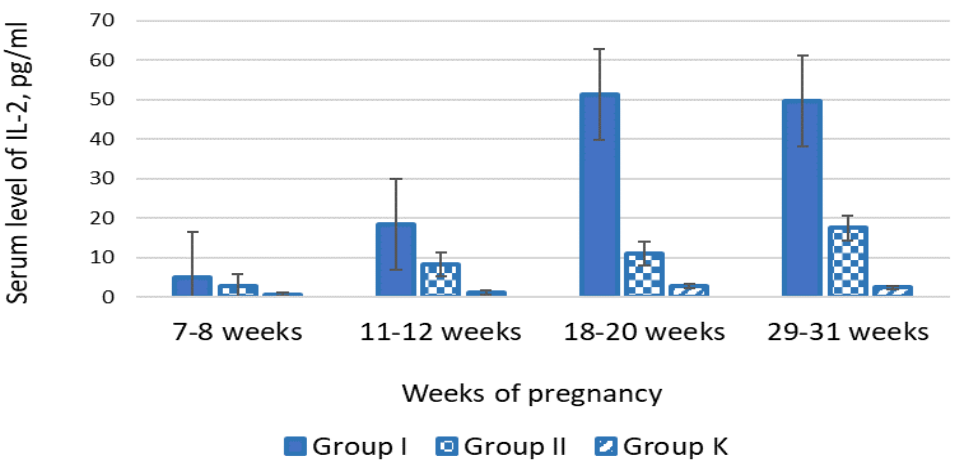

Fig. 4. Serum levels of IL-2 in the dynamics of pregnancy in women of the studied groups

IL-6 is a pleiotropic cytokine mainly produced by monocytes and macrophages, as well as other immune and non-immune cells, including T cells and endothelial cells [10]. IL-6 is a key cytokine that inhibits the proliferation of Treg cells and promotes the differentiation of Th17 cells [12]. IL-6 plays an important role in the initial remodeling of spiral arteries. IL-6 reduction reduces trophoblast invasion and spiral artery remodeling. IL-6 affects not only the implantation of the

embryo and the development of the placenta, but also the immune adaptations necessary for the physiological course of pregnancy. The expression of IL-6 in biological fluids is always accompanied by great variability and depends on many factors affecting the intrauterine state of the fetus, including mixed infection. In addition, being a mediator of subacute and chronic inflammation, IL-6 stimulates neutrophils and macrophages to local production of proinflammatory cytokines [10]. The content of IL-6 in the blood serum of the examined women of group I was statistically significantly higher in the gestation period of 7-8 weeks compared to the similar content in pregnant women of group II and group K by 1.17 ($p<0.01$) and 1.31 ($p<0.01$) times; at 11-12 weeks – 1.29 ($p<0.01$) and 1.43 ($p<0.01$) times; at 18-20 weeks – 1.81 ($p<0.01$) and 1.92 ($p<0.01$) times; in 29-31 weeks – 1.76 ($p<0.01$) and 1.96 ($p<0.01$) times (see table, fig. 5).

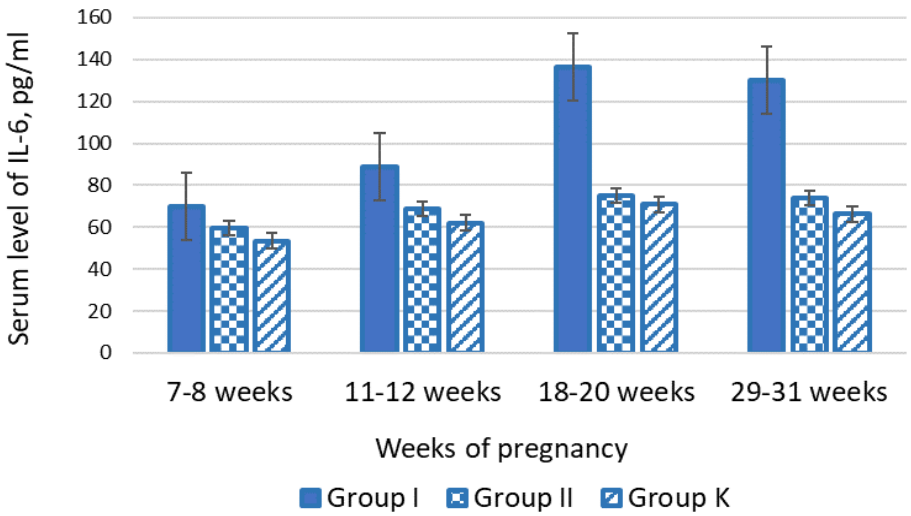

Fig. 5. Serum levels of IL-6 in the dynamics of pregnancy in women of the studied groups

Anti-inflammatory cytokines such as IL-10 and IL-4 may play a compensatory protective role during pregnancy by limiting macrophage production of pro-inflammatory cytokines. Decreased production of IL-4 and IL-10 can increase susceptibility to infections and lead to pregnancy complications and preterm birth [13].

IL-4 is the main cytokine of T-helper type 2 lymphocytes, which plays a key role in the regulation of humoral immune responses. IL-4 is produced not only by placental immune cells, but also by maternal decidual membranes, amniochorial membranes, cytotrophoblasts, and maternal and fetal endothelial cells. Progesterone is an inducer of IL-4 and together they suppress Th1 responses during pregnancy [13]. Levels of IL-4 were increased in pregnant women of group I compared to similar ones in group II by 1.14 ($p<0.01$) times and in group K by 1.59($p<0.01$) times; at 11-12 weeks – 1.86 ($p<0.01$) and 2.90 ($p<0.01$) times; at 18-20 weeks – 2.02 ($p<0.01$) and 3.33 ($p<0.01$) times; in 29-31 weeks – 1.59 ($p<0.01$) and 3.01 ($p<0.01$) times (see table, fig. 6).

The multifunctional anti-inflammatory cytokine IL-10 is produced by macrophages, mast cells, Th2 cells, and regulatory T cells (Tregs). IL-10 controls inflammation, which is important for a successful pregnancy. Tregs are essential for maintaining a healthy pregnancy, and IL-10 is known to mediate Treg development [10]. IL-10 is a Th2 cytokine that suppresses the Th1 immune response by reducing the expression of TNF-α, IFN-γ, and IL-1 [12]. It promotes embryo development by maintaining immunological tolerance. IL-10 is involved in the immunosuppressive response in congestion; high levels of IL-10 in the mother are associated with a successful pregnancy, and vice versa [14].

IL-10 plays an important role in linking the immune response and angiogenesis and suppresses endoplasmic reticulum pressure, promoting protein composition and energy stabilization. Increased endoplasmic reticulum stress leads to activation of proinflammatory reactions and placental abnormalities [12]. In the conducted study, the serum concentration of IL-

10 was statistically significantly reduced in pregnant women of group I compared to similar levels in group II by 1.11 ($p<0.01$) times and in group K by 1.25 ($p<0.01$) times; at 11-12 weeks – 1.25 ($p<0.01$) and 1.33 ($p<0.01$) times; at 18-20 weeks – 1.33 ($p<0.01$) and 1.62 ($p<0.01$) times; in 29-31 weeks – 1.41 ($p<0.01$) and 1.94 ($p<0.01$) times (see table, fig. 7).

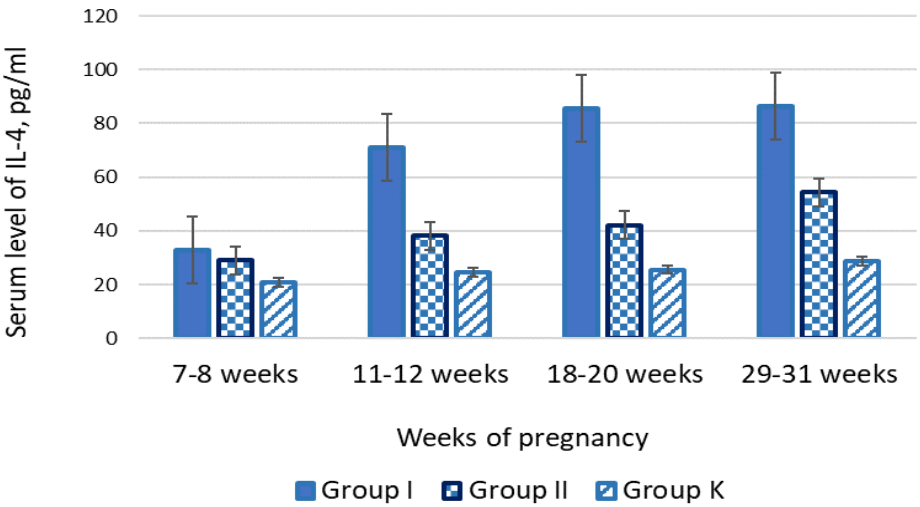

Fig. 6. Serum levels of IL-4 in the dynamics of pregnancy in women of the studied groups

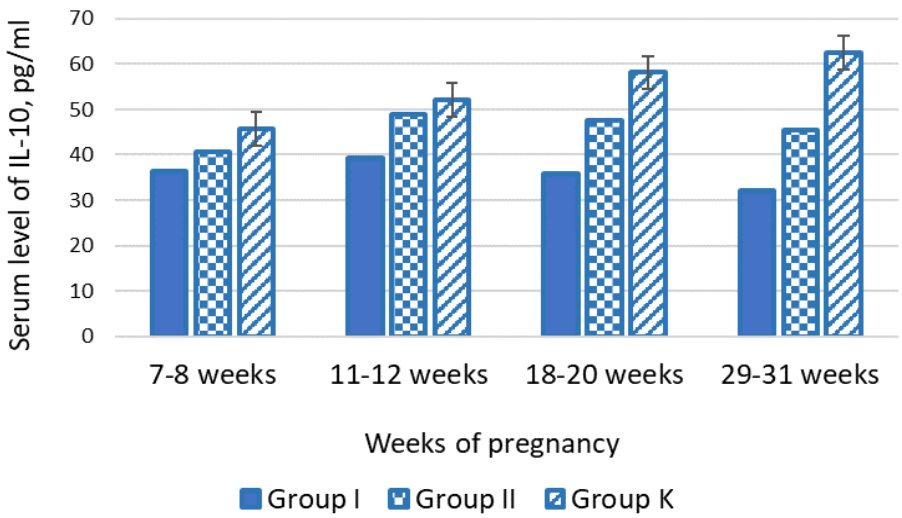

Fig. 7. Serum levels of IL-10 in the dynamics of pregnancy in women of the studied groups

The level of CRP gradually increases during pregnancy and reaches a peak at birth; CRP cannot cross the placental barrier and affect the fetus. CRP is widely used in clinical practice as a nonspecific indicator of the acute phase of inflammation, given its rapid production by the liver and release into the circulation and its stimulation by several cytokines, including IL-6, IL-1β, and TNF-α. CRP also helps the body recognize the presence and severity of infections and is used as an indicator of mild inflammation in chronic infections and chronic diseases [15]. Serum levels of CRP were increased at 7-8 weeks of gestation in the examined pregnant women of group I compared to similar ones in group II by 1.44 ($p<0.01$) times and in group K by 1.79 ($p<0.01$) times; at 11-12 weeks – 1.42 ($p<0.01$) and 1.83 ($p<0.01$) times, respectively; at 18-20 weeks – 1.26 ($p<0.01$) and 1.97 ($p<0.01$) times; in 29-31 weeks – 1.30 ($p<0.01$) and 1.91 ($p<0.01$) times (see table, fig. 8).

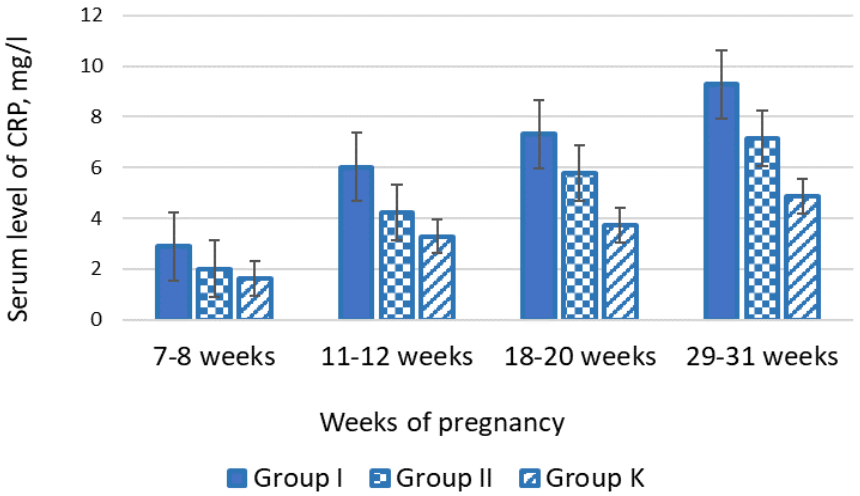

Fig. 8. Serum levels of CRP in the dynamics of pregnancy in women of the studied groups.

In this study, for the first time, the dynamics of serum cytokine and CRP levels in women of late reproductive age with induced ART cycles was studied. All of the pregnancies ended in labor, yet the pregnancies occurred amid altered immune reactivity, manifested by abnormal levels of signaling molecules such as cytokines and CRP, compared to women of the same age but with natural conception. Abnormal production of pro- and anti-inflammatory cytokines, CRP can be a factor in placental dysfunction, gestational complications and premature birth in induced pregnancy in women of advanced reproductive age. The revealed statistically significant differences between the cytokine profile and the levels of CRP between women with induced pregnancy of active and advanced reproductive age indicate the possible role of reproductive aging in the occurrence of placental abnormalities and the development of placenta-associated complications of pregnancy.

Conclusions from the conducted research

An important characteristic of successful implantation and successful continuation and termination of pregnancy is inflammation. Serum levels of IL-1β, TNF-α, INF-γ, IL-2, IL-4, IL-6 and CRP during ART-induced pregnancy in women of advanced reproductive age differ from similar levels during ART-induced pregnancy in women of active reproductive age and throughout pregnancy after natural conception in women of advanced reproductive age with higher values, while the serum IL-10 content is lower. Abnormal inflammation and reproductive aging can be a factor in obstetric and perinatal complications of pregnancy induced in ART cycles in women of advanced reproductive age.

Prospects for further developments in this direction

Correlations of serum cytokine levels in women of advanced reproductive age with obstetric and perinatal outcomes require further study.

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