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## EFFECT OF THE COMPLEX OF CONTRICAL AND HEPARIN ON CHANGE OF IMMUNOLOGICAL INDICATORS IN WOMEN IN EARLY PERIODS OF PREGNANCY

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✓ ***Resume***

***The work studied the effect of a complex of counterkals and heparin on changes in immunological parameters in women in early pregnancy with an excessive pro-inflammatory immune response and insufficient corrective response of protease inhibitors and TGF-β1. It was concluded that an excessive pro-inflammatory immune response in early pregnancy and an insufficient corrective response of protease inhibitors and TGF-β1 can create unfavorable conditions for the course of early pregnancy and the development of miscarriages. The use of pregravid treatment with a complex of counterkal and heparin helps to reduce the excessive pro-inflammatory immune response in the early stages of pregnancy, as well as to restore protease inhibitors and TGF-β1, which can contribute to a favorable course of pregnancy in the early stages and the development of a full-fledged pregnancy.***

***Key words: interleukins, protease inhibitors, early pregnancy, miscarriage, infections of the genitourinary system, contrikal, heparin.***

## ВЛИЯНИЕ КОМПЛЕКСА КОНТРИКАЛ И ГЕПАРИН НА ИЗМЕНЕНИЕ ИММУНОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ У ЖЕНЩИН НА РАННИХ СРОКАХ БЕРЕМЕННОСТИ

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✓ ***Резюме***

***В работе изучалось влияние комплекса контрикал и гепарин на изменение иммунологических показателей у женщин на ранних сроках беременности с чрезмерной провоспалительной иммунной реакцией и недостаточной корригирующей реакцией ингибиторов протеаз и TGF-β1. Сделано заключение, что чрезмерная провоспалительная иммунная реакция в ранние сроки беременности и недостаточная корригирующая реакция ингибиторов протеаз и TGF-β1 может создавать неблагоприятные условия течению беременности в ранние сроки и развитию выкидышей. Применение прегравидарного лечения комплексом контрикал и гепарин способствует снижению чрезмерной провоспалительной иммунной реакции в ранние сроки беременности, а также восстановлению ингибиторов протеаз и TGF-β1, что может способствовать благоприятному течению беременности в ранние сроки и развитию полноценной беременности.***

***Ключевые слова: интерлейкины, ингибиторы протеаз, ранние сроки беременности, невынашивание беременности, инфекции мочеполовой системы, контрикал, гепарин.***

## АЁЛЛАРДА ҲОМИЛАДОРЛИКНИНГ ЭРТА ДАВРИДАГИ КОНТРИКАЛ ВА ГЕПАРИН КОМПЛЕКСИ ТАЪСИРИДА ИММУНОЛОГИК КЎРСАТГИЧЛАРНИНГ ЎЗГАРИШИ

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***Мақолада ҳомиладорликнинг эрта даврида ҳаддан ташқари яллигланишга қарши иммун реакцияси, протеаза ингибиторлари ва TGF-β1 нинг тузатувчи реакцияси етарли бўлмаган аёлларда иммунологик параметрларнинг ўзгаришига контрикал ва гепарин комплексининг таъсири ўрганилди. Эрта ҳомиладорлик давридаги ҳаддан ташқари яллигланишга қарши иммунитет реакцияси ва TGF-β1 ҳамда протеаза ингибиторларининг тузатувчи реакцияси етишмовчилиги, эрта ҳомиладорликнинг кечишига салбий таъсир кўрсатиши ва ҳомиланинг тушишига олиб келиши мумкинлиги тўғрисида хулоса чиқарилди. Контрикал ва гепарин комплекси билан прегравидар даволашни қўлланиши, ҳомиладорликнинг дастлабки босқичларида ҳаддан ташқари яллигланишга қарши иммун реакциясини камайтиришга, шунингдек протеаза ингибиторлари ва TGF-β1 ни тиклашга ёрдам беради, бу эса ҳомиладорликнинг эрта босқичида қулай кечишига ва ҳомиладорликнинг тўлиқ ривожланишига шароит яратади.***

***Калит сўзлар: интерлейкинлар, протеаза ингибиторлари, эрта ҳомиладорлик, урогенитал тизимининг инфекциялари, контрикал, гепарин.***

## Relevance

In addition to their antiprotease activity, protease inhibitors also have other properties that contribute to the termination of the inflammatory process, including modulation of cytokine expression, signal transduction, and tissue remodeling [9, 10].

An increase in the endogenous release of interleukin-10 was found after therapy with aprotinin, an inhibitor of serine proteases. This study demonstrates the unique anti-inflammatory activity of aprotinin, which may be of clinical significance [4]. Low doses of aprotinin administered to humans have also been shown to reduce systemic TNF release and subsequent activation of CD11b by neutrophils. This effect of aprotinin is similar to that found in a comparable group of patients receiving glucocorticoid alone (methylprednisolone). These data demonstrate that aprotinin has anti-inflammatory effects in humans [4]. In addition, aprotinin has been found to inhibit plasmin-mediated fibrinolysis and many enzymatic mediators that contribute to the generalized inflammatory response. Some, but not all, studies have shown that aprotinin effectively reduces the production of IL-6 [2].

Presumably, the protease inhibitor counterkal can increase the biological effect of TGF-β by releasing it from the complex with alpha-2-macroglobulin [6]. In addition, counterkal inhibits inflammatory markers, trypsin, pancreatic elastase, leukocyte elastase, as well as the production of TNF-alpha and interleukin 1, 8 and 6. In addition, it inhibits the secretion of pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-10 , IL-11, TNF, NO, PAF [7, 8].

TGF-β1 electrophoresis has shown that protease inhibitors can protect TGF-β1 from proteolytic degradation by plasmin and trypsin [6].

Studies have shown that the combined use of aprotinin and heparin decreases IL-6 and increases the release of IL-10, while IL-8 is not affected. Further research should investigate the effects of combined use to reduce the release of inflammatory cytokines [3]. In addition, it has been proven that the combined use of aprotinin together with heparin helps to reduce the activation of complement, coagulation and fibrinolysis. Therefore, the authors recommend using both of these drugs together to achieve the maximum reduction in blood activation [1].

**The aim of the study:** to study the effect of a complex of counterkal and heparin on changes in immunological parameters in women in early pregnancy.

## Material and methods

In the work, 46 women were examined, who were divided into 3 groups. Group 1 included 20 women with a full pregnancy and full delivery, who had no infections of the genitourinary system before pregnancy. Group 2 consisted of 15 women who had miscarriages up to 12 weeks of pregnancy, before pregnancy they did not have infections of the genitourinary system, but had an excessive pro-inflammatory immune response. Group 3 included 11 women who had no infections of the genitourinary system before pregnancy, but due to changes in immunological parameters and blood protease inhibitors, had an excessive pro-inflammatory immune response and the potential for miscarriages before 12 weeks of pregnancy. During the period of pregravid preparation, these women received protease inhibitor contrakal at a dose of 10 thousand units, which is injected intravenously in a syringe at a ratio of 1: 2 with a standard solvent once a day and low molecular weight heparin clexane at a dose of 20 mg once a day for 15 days under the control of the prothrombin index.

In the blood of women before pregnancy, before 6 and up to 12 weeks of pregnancy, the following parameters were determined by ELISA: pro-inflammatory - interleukin-1β (IL-1) and tumor necrosis factor-α (TNF-α), and anti-inflammatory - interleukin-10 (IL- 10) with the use of test systems of ZAO "Vector-Best" Russia, also transforming growth factor-β1 (TGF-β1) using test systems "DRG" Germany. In addition, the protease inhibitors α-1-anti-trypsin and α-2-macroglobulin were determined using test systems "Sentinel" Italy.

**Result and discussion**

According to the results of our data, it was found (table) that before pregnancy in women of group 2, the indicator of proinflammatory interleukin TNF-α was significantly and reliably more than 2.3 times higher than in women of group 1 with a full pregnancy. In women of group 3 with the potential for miscarriages, before pregnancy, TNF-α in the blood, as well as in women of group 2, was significantly more than 2.2 times higher than in women of group 1. At the same time, the result of TNF-α in women of group 1 up to 6 weeks of pregnancy was significantly higher than the indicator before pregnancy. The level of this indicator in women of group 2 up to 6 weeks of pregnancy was significantly and reliably more than 2.6 times higher than in women of group 1. In women of group 3 who received pregravid treatment with a complex of counterkal and heparin, the values of proinflammatory interleukin TNF-α before 6 weeks of pregnancy were significantly more than 1.6 times higher than in women of group 1. In the same group, TNF-α was 1.7 times significantly lower than in women in group 2 who did not receive treatment with a complex of counterkal and heparin. When examining women of group 1 before 12 weeks of pregnancy, TNF-α was significantly higher than the same indicator before pregnancy and slightly more than before 6 weeks of pregnancy, but significantly higher than similar results before pregnancy. In women of 2 groups who have miscarriages

Before 12 weeks of pregnancy, the TNF-α indicator was significantly and reliably more than 2.8 times higher than in women of group 1.

At the same time, in women of group 3 who received pregravid treatment with a complex of counterkal and heparin, the values of proinflammatory interleukin TNF-α before 12 weeks of pregnancy were significantly 1.7 times higher than in women of group 1 and also significantly 1.7 times, but lower , compared with women in group 2 who did not receive treatment.

In the study of pro-inflammatory IL-1β in women of group 2 before pregnancy, it was found that this indicator had similar changes as TNF-α, significantly and reliably more than 3.1 times higher than in women of group 1 with a full pregnancy. In women of group 3, before potential potential miscarriages, IL-1β had similar changes as in women in group 2, and, similarly to the TNF-α indicator, was at a level significantly 2.9 times higher than in women of group 1. At the same time, the values of IL-1β in women of group 1 up to 6 weeks of pregnancy were significantly higher than the results before pregnancy. At the same time, the level of this indicator in women in group 2 up to 6 weeks of pregnancy was more than 2.7 times higher than in women in group 1, which was also similar to those changes in TNF-α. In women of group 3 who received pregravid treatment with a complex of counterkal and heparin, the level of pro-inflammatory interleukin IL-1β before 6 weeks of pregnancy was significantly more than 1.8 times higher than in women of group 1. However, it was reliably more than 1.5 times less than in women in group 2 who did not receive treatment. In the study of IL-1β in women of group 1 up to 12 weeks of pregnancy, this indicator was significantly higher than the same result before pregnancy and slightly more than before 6 weeks of pregnancy, but significantly higher than similar results before pregnancy. In women of group 2 who miscarried before 12 weeks of pregnancy, the IL-1β indicator was also significantly and reliably more than 2.6 times higher than in women of group 1. At the same time, in women of group 3 up to 12 weeks of pregnancy who received pregravid treatment, the IL-1β indicator was more than 1.7 times higher than in women of group 1 and reliably more than 1.5 times lower than in women of group 2 (table).

The IL-10 index in women of group 2 before pregnancy was significantly more than 1.5 times lower compared to similar results for women in group 1 with a full pregnancy. In women of group 3 with the potential for miscarriages, IL-10 before pregnancy had similar changes as in women of group 2 and was significantly more than 1.6 times higher than in women of group 1. At the same time, in the blood of women of group 1, the IL-10 indicator before 6 weeks of pregnancy was insignificantly lower than similar results before pregnancy, and in women of the same group before 12 weeks of pregnancy, this indicator was insignificantly less than in women before 6 weeks of pregnancy and significantly lower the same results before pregnancy. In women of group 2 up to 6 weeks of pregnancy, IL-10 was

significantly 1.7 times less and even before 12 weeks of pregnancy 2.4 times less in relation to the indicators before pregnancy in the same group. In addition, IL-10 in women of group 2, up to 6 weeks of pregnancy by 2.1 times and up to 12 weeks by 2.3 times was significantly lower than similar indicators of group 1. At the same time, in women of the 3rd group who received pregravid treatment, IL-10 up to 6 weeks of pregnancy was more than 1.4 times higher, and before 12 weeks of pregnancy it was significantly more than 1.5 times higher than in women of the 2nd group who did not receive treatment. complex kontrikal and heparin (table).

Table.

Changes in the indices of pro-inflammatory (TNF-α, IL-1β), anti-inflammatory (IL-10) interleukins, TGF-β1 and protease inhibitors in the blood of women in the surveyed groups.

| Investigated indicators | Group | Before pregnancy | Up to 6 weeks pregnant | Up to 12 weeks pregnant |
|---|---|---|---|---|
| TNF-α pg / ml | 1 | 6,2±0,8 | 9,7±1,2* | 11,9±1,5* |
| | 2 | 14,8±1,6$^{o}$ | 25,5±2,7*$^{o}$ | 32,8±4,1*$^{o}$ |
| | 3 | 13,4±1,4$^{o}$ | 15,3±1,6$^{o+}$ | 20,7±1,8*$^{o+}$ |
| IL-1β pg / ml | 1 | 3,7±0,4 | 7,2 ± 0,9* | 10,1±1,2* |
| | 2 | 11,6±1,5$^{o}$ | 19,4 ± 2,3*$^{o}$ | 25,9±3,1*$^{o}$ |
| | 3 | 10,7±0,9$^{o}$ | 12,6 ± 1,3$^{o+}$ | 17,4±1,8*$^{o+}$ |
| IL-10 pg / ml | 1 | 9,3±1,2 | 7,4±0,8 | 5,9±0,7* |
| | 2 | 6,1±0,7$^{o}$ | 3,5±0,5*$^{o}$ | 2,6±0,4*$^{o}$ |
| | 3 | 5,7±0,6$^{o}$ | 4,8±0,5$^{o}$ | 3,9±0,4*$^{o+}$ |
| TGF-β1 ng / ml | 1 | 32,6 ± 4,5 | 49,8 ± 5,7* | 58,6±7,3 * |
| | 2 | 25,7 ± 2,5 | 19,6 ± 2,1$^{o}$ | 15,8±1,7$^{o}$ |
| | 3 | 27,3 ± 3,1 | 34,2 ± 3,7$^{o}$ | 41,4±4,5*$^{o+}$ |
| α -1-anti-trypsin mg / dl | 1 | 136±14,8 | 179±18,6 | 198±21,4* |
| | 2 | 97±10,3$^{o}$ | 65±7,1*$^{o}$ | 54±6,2*$^{o}$ |
| | 3 | 109±11,4 | 136±14,2$^{o}$ | 157±17,5*$^{+}$ |
| α -2 -macro-globulin mg / dl | 1 | 284±30,6 | 297±31,6 | 315±33,9 |
| | 2 | 257±27,2 | 239±25,8 | 228±23,6 |
| | 3 | 266±28,1 | 273±29,7 | 298±30,4 |

*Note: 1- women who have a full pregnancy; 2 - women who had miscarriages before 12 weeks of pregnancy; 3 - women who have the potential for miscarriages before 12 weeks of pregnancy and who received pregravid treatment with a complex of counterkal and heparin.*

** - significantly different values to the indicators before pregnancy.*

*o - significantly different values to the indicators of group 1.*

*+ - significantly different values to the indicators of group 2.*

According to the results of the study of TGF-β1 in the blood of women of group 1, up to 6 weeks of pregnancy, this indicator was significantly higher than similar results before pregnancy. In the same group, in women before 12 weeks of pregnancy, the TGF-β1 indicator was insignificantly higher than in women before 6 weeks of pregnancy and significantly higher than the same indicators before pregnancy. In women in group 2, the TGF-β1 index before pregnancy was insignificantly lower than in women in group 1. In the same group, in women before 6 weeks of pregnancy, TGF-β1 was significantly more than 2.5 times less than in women of group 1, but slightly lower than the indicators before pregnancy in the same group. Before 12 weeks of pregnancy in women of group 2, TGF-β1 was significantly more than 3.7 times less than similar results for women in group 1, and also significantly lower than the indicators before pregnancy in the same group. In women of group 3 who received pregravid treatment up to 6 weeks of pregnancy, TGF-β1 was significantly 1.8 times, and before 12 weeks of pregnancy, it was significantly 2.6 times more than in women of group 2 who did not receive treatment with a complex of counterkal and heparin (Table .).

The data obtained from the study of α-1-anti-trypsin showed that in women of group 1 up to 6 weeks of pregnancy, this indicator was insignificantly higher compared to the data before pregnancy. In women of the same group, before 12 weeks of pregnancy, the α -1-anti-trypsin index was insignificantly higher than before 6 weeks of pregnancy, and also significantly more similar results before pregnancy. In addition, in the study of α-1-anti-trypsin in women of group 2, the index of α-1-anti-trypsin before pregnancy was significantly 1.4 times lower than in women of group 1. Also, in women of group 2 up to 6 weeks of pregnancy, the result of α-1-anti-trypsin was significantly and reliably 2.8 times less than similar data for women in group 1 and reliably 1.5 times less than the same data before pregnancy in the same group. In addition, in women of group 2 up to 12 weeks of pregnancy, α-1-anti-trypsin was also significantly 3.7 times lower than those of women in group 1 and significantly 1.8 times more results before pregnancy in the same group. At the same time, in women of group 3 up to 6 weeks of pregnancy, who received pregravid treatment, α-1-anti-trypsin was significantly 1.8 times, and up to 12 weeks of pregnancy, it was significantly 2.6 times more than in women of group 2 who did not receive treatment with a complex of counterkal and heparin (table).

The results of the study of α-2-macro-globulin showed that in women of the 1st group there was a slight increase in this indicator up to 6 weeks of pregnancy and even more up to 12 weeks of pregnancy. In women of group 2, the opposite dynamics of changes in α-2 -macro-globulin was observed, which manifested itself in an insignificant decrease in the results up to 6 weeks and in an even greater decrease up to 12 weeks of pregnancy in relation to the same results before pregnancy of the same group. In women of group 3, as well as in the first group, there was a slight increase in α-2-macro-globulin up to 6 weeks of pregnancy and even more up to 12 weeks of pregnancy (table).

From the data obtained, it can be seen that the level of TNF-α and IL-1β in the blood, both in women of group 1 with a full pregnancy, and in group 2 who had miscarriages before 12 weeks of pregnancy was significantly higher up to 6 weeks of pregnancy and even more up to 12 weeks of pregnancy compared with those before pregnancy. At the same time, the indicators of TNF-α, IL-1β in women of group 2 were significantly and reliably higher than in women of group 1. At the same time, in women of group 3 with the potential for miscarriages and receiving pregravid treatment with a complex of counterkal and heparin, TNF-α, IL-1β values were significantly higher than in women of group 1, but significantly lower than in women of group 2 who did not receive treatment. ...

At the same time, the level of IL-10 in the blood, both in women of group 1 and group 2, had the opposite direction and decreased in relation to the indicators before pregnancy. Unreliable up to 6 weeks of pregnancy and reliably up to 12 weeks of pregnancy in women of group 1 and reliably up to 6 and 12 weeks of pregnancy in women of group 2. In addition, it was found that all IL-10 indicators in women of group 2 before pregnancy, up to 6 and 12 weeks of pregnancy were significantly and reliably lower than similar results in women of group 1. At the same time, the use of pregravid treatment with a complex of counterkal and heparin in women of group 3 with the potential for miscarriages caused an increase in IL-10 in women up to 6 weeks and up to 12 weeks of pregnancy, compared with women in group 2 who did not receive treatment.

It was also found that the TGF-β1 index in the blood of women of group 1 significantly increased up to 6 weeks of pregnancy and even more up to 12 weeks of pregnancy, compared with similar indicators before pregnancy. At the same time, in women of group 2, TGF-β1 also had the opposite direction and decreased insignificantly up to 6 and 12 weeks of pregnancy in relation to the results before pregnancy. At the same time, in women of the 2nd group, the TGF-β1 indices up to 6 and 12 weeks of pregnancy were significantly lower than the same results of the 1st group. However, in women of group 3 who received pregravid treatment, TGF-β1 up to 6 weeks of pregnancy and up to 12 weeks of pregnancy was significantly higher than in women of group 2 who did not receive treatment with a complex of counterkal and heparin.

In women of group 2, when studying protease inhibitors, a greater change in α -1-anti-trypsin was noted, which was expressed in a significant decrease in this indicator before pregnancy, as well as before 6 and 12 weeks of pregnancy in relation to similar results for women in group 1. In addition, there was a significant decrease in α -1-anti-trypsin before 6 and 12 weeks of gestation in relation to the results before pregnancy. In women of group 3 who received pregravid treatment, the α-1-anti-trypsin values up to 6 weeks and up to 12 weeks of pregnancy were higher than in women of group 2 who did not receive treatment with a complex of counterkal and heparin. Changes in α-2-macro-globulin were noted to a lesser extent. This was manifested in an insignificant increase in this indicator in women of group 1 up to 6 weeks of pregnancy and more up to 12 weeks of pregnancy. At the same time, in women of group 2 up to 6 and 12 weeks of pregnancy, there was a slight decrease in this

indicator, compared with the results before pregnancy in the same group. At the same time, women in group 3 showed a slight increase in α-2-macro-globulin up to 6 weeks of gestation and even more up to 12 weeks of pregnancy.

Thus, the presence of an excessive pro-inflammatory immune response in early pregnancy and an insufficient corrective response of protease inhibitors and TGF-β1 may contribute to an unfavorable course of early pregnancy and the development of miscarriages. The use of pregravid treatment with a complex of counterkal and heparin helps to reduce the excessive pro-inflammatory immune response in the early stages of pregnancy, as well as to restore protease inhibitors and TGF-β1, which can contribute to a favorable course of pregnancy in the early stages and the development of a full-fledged pregnancy.

## Conclusions

An excessive pro-inflammatory immune response in early pregnancy and an insufficient corrective response of protease inhibitors and TGF-β1 can create unfavorable conditions for the course of early pregnancy and the development of miscarriages. The use of pregravid treatment with a complex of counterkal and heparin helps to reduce the excessive pro-inflammatory immune response in the early stages of pregnancy, as well as to restore protease inhibitors and TGF-β1, which can contribute to a favorable course of pregnancy in the early stages and the development of a full-fledged pregnancy.

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