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## Local inflammatory factors in pregnant women with various methods of cervical insufficiency treatment

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*Abstract: the reasons for the formation of cervical insufficiency are considered to be different from violation of the ratio of connective tissue elements due to its genetic characteristics to hormonal imbalance, and the predominance of pro-inflammatory factors of the immune system. A special attention is devoted to clinical situations, when cervical insufficiency was diagnosed in terms 22-24 weeks, the treatment means an alternative between emergency cerclage and obstetric pessary. The goal of study – to compare dynamic of vaginal microbiota and local cervical immune factors by use of different cervical insufficiency treatment methods. Materials and methods. 81 pregnant with cervical insufficiency, diagnosed in term 22-24 weeks were observed, 47 pregnant treated by cerclage procedure (group A), and 34 were fitted with an obstetric pessary (group B). 30 healthy pregnant women in the period of 22 weeks formed group C. In all patients before treatment and every two weeks after it microscopy of vaginal discharges according to Hay/Ison criteria and evaluation of cervical cytokines were performed. Results. The balance by obstetric pessary use of type I and type III by Hay-Ison criteria being similar before treatment with pregnancy prolongation is changing dramatically to the prevalence of bacterial vaginosis by use of obstetric pessary – from 30,3% and 21,2% in 2 weeks to 25,0% and 41,7% in 6 weeks, by cerclage – from 43,5% and 14,9% in 2 weeks to 30,3% and 17,5% in 6 weeks. Patients with cervical insufficiency have increased concentration of IL-6 and IL-10, but by use of obstetrical pessary additionally growth of IL-8 from 42,3 pg/ml in 2 weeks to 187,6 pg/ml in 6 weeks is registered as well as decreasing of SLPI from 1,5 µg/ml to 0,6 µg/ml. Both changes show progression of inflammation and are associated with worth pregnancy outcomes. In the same time, cerclage is associated with growth of SLPI from 1,9 µg/ml to 4,3 µg/ml, what is a marker of adequate immune reaction by pregnancy. There is a difference between the groups of cerclage and obstetric pessary in dynamic of microbiota changes – a tendency to increasing of laboratory criteria of bacterial vaginosis frequency in group of obstetric pessary in 2 weeks becomes significant in 4 and more in 6 weeks comparing with group of cerclage. Proper to cervical insufficiency high concentration of proinflammatory IL-6 and IL-10 by use of obstetrical pessary is complicated by increasing of IL-8 and decreasing of SLPI, what means an activation of cervical inflammation, by cerclage – a increasing of SLPI is observed, what is favourable for pregnancy.*

**Keywords:** [Interleukin-6](#); [Interleukin-8](#); [Interleukin-10](#); [Vaginosis Bacterial](#); [Gardnerella Vaginalis](#); [Lactobacillus](#).

## Introduction

Cervical insufficiency (CI) is a pregnancy complication, a painless shortening and ripening of cervix in second pregnancy trimester, a reason of every third case of recurrent abortions and preterm delivery. The frequency of CI is not more than 1% of obstetric populations, but medical, social and economic consequences of it are much greater. Recurrent pregnancy losses and very preterm delivery caused by CI also have a powerful influence on psychological condition of person and family (Han, 2020). At the same time, the etiology of CI is still uncertain and it is still a controversial disease in diagnosis and treatment. The reasons for the formation of CI are considered to be different from violation of the ratio of connective tissue elements due to its genetic characteristics to hormonal imbalance, and the predominance of pro-inflammatory factors of the immune system (Bila & Chernega, 2023).

More than 2 million procedures of cervical cerclages are registered annually in the world, called to prevent preterm delivery. The considered mechanism include structural support of cervix and maintenance of the endocervical mucus plug role as a barrier to infection (Hodges Morton, 2022).

A special attention is devoted to clinical situations, when CI was diagnosed in terms 22-24 weeks, the treatment here means an alternative between emergency cerclage and obstetric pessary. Knowledge about clinical effectiveness and safety for mother and a newborn of an emergency cerclage vary from high ability to prevent very preterm labour (Kaur, 2023) to an increased level of neonatal infection, thus – of mortality and morbidity level (Alfirevic, 2017). Anyway, Wei (2023) reported, that emergency cerclage comparing to expectant management results in decreasing of preterm labour rate, early preterm labour rate, low Apgar score and increasing of neonatal survive rate.

D.Konkov (2022) published results of perforated Arabin pessary effectiveness study to prevent preterm labour in patients of high risk. They have reported about two times decreasing of labour before 37 weeks rate, three times – before 35 weeks, better perinatal outcomes by use of pessary comparing with expectation group.

There is a lack of studies devoted to comparing of effectiveness of both methods from the point of

view pregnancy prolongation and perinatal outcomes. One of them is basing on 20 observations, divided on pessary and suture group, have found any difference both in terms of delivery and in neonatal outcomes. But considering surgical risks, like as anesthesia, need of long hospitalisation, economic costs, authors propose to speak about pessary benefits. The limitation of this study is a small number of patients (Pizzicaroli, 2021).

## Aim

The goal of study – to compare dynamic of vaginal microbiota and local cervical immune factors by use of different cervical insufficiency treatment methods.

## Materials and methods

81 pregnant women with CI, diagnosed in term 22-24 gestational weeks, were divided into 2 groups. 47 pregnant treated by cerclage procedure (group A), and 34 were fitted with an obstetric pessary (group B) in the Perinatal Center of Kyiv. For comparison, 30 pregnant women in the period of 22 weeks, taken ambulatory prenatal care in Kyiv Perinatal Center (group C) were invited.

In all patients before treatment and every two weeks after it before reaching the gestational term 34 weeks the microscopy of vaginal discharges according to Hay/Ison criteria were performed (Abau Chacra, 2024). The material was got from vagina by a sterile brush, coloured by Gram and by light microscopy at magnification of 1000 the balance of bacteria types was estimated. Smear type 0 means lack of bacteria, that is proper to consequences of antibacterial treatment, type 1 – domination of Lactobacilles, type 2 – equal combination of lactobacilles and Gardnerella morphology, type 3 – domination of Gardnerella and type 4 – prevalence of aerobic pathogenic biotops. The difference between groups in frequency of biocenosis types was estimated, as well as the dynamic of changes in each group while pregnancy duration.

Before treatment and every 2 weeks after it the cervical concentration of IL-6, IL-8, IL-10 and SLPI were evaluated by ELISA method, using Semen Technology kit, USA.

As some patients had preterm delivery, they were excluded from study – in 2 weeks group A had 46 patients, group D – 33 pregnant, in 4 weeks – 43 and 30 and in 6 weeks – 40 and 24 accordingly.

The statistical analysis was performed using Student criteria, the difference between groups and between results of one group was significant by  $p$  value  $\leq 0,05$ . For statistical analysis a program package Statistica 2020 was used.

### Results

An important role in the progression of immune imbalance belongs to the microflora of the vagina, which was studied in the dynamics of the progression of pregnancy.

Before procedure of CI treatment method, the distribution of pregnant women according to the type of discharge microscopy according to the Hyw-Ison criteria did not differ between groups, including in pregnant women with CI and healthy pregnant (tab.1). 53.2% of pregnant women of group A, 52.9% of group B, 60.0% of group C had a normal type of smear, and the type of bacterial vaginosis was detected in 12.7%, 14.7% and 8.8% of pregnant in accordance.

**Table 1.** Vaginal microscopy results according Hay-Ison criteria in pregnant with CI

| Type                           | Group A                 | Group B                  | Group C     |
|--------------------------------|-------------------------|--------------------------|-------------|
| Before treatment               |                         |                          | 22 weeks    |
| N                              | 47                      | 34                       | 30          |
| Type 0                         | 1 (2,1%)                | 1 (2,9%)                 | 1 (3,3%)    |
| Type I (normal)                | 25 (53,2%)              | 18 (52,9%)               | 18 (60,0%)  |
| Type II (mixed)                | 10 (21,3%)              | 6 (17,6 %)               | 5 (14,7%)   |
| Type III (bacterial vaginosis) | 6 (12,8%)               | 5 (14,7%)                | 3 (8,8%)    |
| Type IV (aerobic vaginitis)    | 5 (10,6%)               | 4 (11,8%)                | 3 (8,8%)    |
| In 2 weeks                     |                         |                          | 24 weeks    |
| N                              | 46                      | 33                       | 30          |
| Type 0                         | 1 (2,2%)                | –                        | –           |
| Type I (normal)                | 20 (43,5%)              | 10 (30,3%) <sup>§</sup>  | 19 (63,3%)  |
| Type II (mixed)                | 16 (34,8%)              | 12 (36,4%)               | 4 (13,3%)   |
| Type III (bacterial vaginosis) | 7 (14,9%)               | 7 (21,2%)                | 4 (13,3%)   |
| Type IV (aerobic vaginitis)    | 2 (4,4)                 | 4 (12,1%)                | 3 (10,0%)   |
| In 4 weeks                     |                         |                          | 26 weeks    |
| N                              | 43                      | 30                       | 30          |
| Type 0                         | –                       | –                        | 1 (3,3%)    |
| Type I (normal)                | 18 (41,9%)              | 8 (26,7%) <sup>§#</sup>  | 17 (56,7%)  |
| Type II (mixed)                | 14 (32,6%)              | 10 (33,3%)               | 7 (23,3%)   |
| Type III (bacterial vaginosis) | 7(16,2%) <sup>§</sup>   | 8 (26,7%) <sup>§#</sup>  | 2 (6,7%)    |
| Type IV (aerobic vaginitis)    | 4 (9,3%)                | 4 (13,3%)                | 3 (10,0%)   |
| In 6 weeks                     |                         |                          | 28 weeks    |
| N                              | 40                      | 24                       | 30          |
| Type 0                         | –                       | –                        | –           |
| Type I (normal)                | 12 (30,0%) <sup>§</sup> | 6 (25,0%) <sup>§</sup>   | 15 (50,0 %) |
| Type II (mixed)                | 13 (32,5%) <sup>§</sup> | 2 (8,3%) <sup>#</sup>    | 8 (3,3%)    |
| Type III (bacterial vaginosis) | 7 (17,5%)               | 10 (41,7%) <sup>§#</sup> | 3 (10,0%)   |
| Type IV (aerobic vaginitis)    | 3 (7,5%)                | 2 (8,3%)                 | 4 (13,3%)   |

§ –  $p \leq 0,05$  comparing to group C

# –  $p \leq 0,05$  comparing to group A

As early as two weeks after using the treatment method, group B differed from the control group in terms of the proportion of pregnant women with a normal type of smear – 30.3% versus 63.3% in group C, in group A a statistically insignificant trend towards a decrease in the proportion of a normal type of smear was noted – 43, 5%. A trend towards to increasing of part of pregnant women with bacterial vaginosis was also revealed – up to 21.2% in the group of pregnant with obstetric pessary used for correction. Among healthy pregnant women, only 13.3% of participants had this type of microflora, but in the cerclage group – 14.9%, that is, no more.

4 weeks after correction of CI, the frequency of type III detected in the microcopy increases in both groups, but in the obstetric pessary group it reached 26.7%, and in the cerclage group – 16.2%. In the group of healthy pregnant women, it was 6.7% in the corresponding term. It is also important to note that in this period, a decrease in the proportion of pregnant women with a normal type of smear was noted in the obstetric pessary group – to 26.7% against 41.9% in the cerclage group and 56.7% in the healthy pregnant group.

After 6 weeks, the share of pregnant women with bacterial vaginosis in group B increased even more – up to 41.7%, in group A and in the con-

trol group during these 2 weeks it almost did not change – 17.5% and 10.0%, respectively. In group B, the share of pregnant women with a normal type of microscopic smear did not change (25%), in group A it probably decreased from 41.9% to 30%, and in the group of healthy pregnant women it remained at the level of 50%.

The frequency of aerobic smear type did not differ between the groups of pregnant women with CI and healthy pregnant women, nor in the dynamics of pregnancy prolongation from the moment of correction of CI.

Thus, there is a significant difference between the groups of cerclage and obstetric pessary – against the background of obstetric pessary, already 2 weeks after the application of the correction method, a tendency to increase laboratory criterion of bacterial vaginosis is observed when compared with the group of cerclage and the group of healthy pregnant women. This difference becomes statistically significant up to 4 weeks and increases up to 6 weeks.

To study the influence of the applied treatment method on the content of local immune factors, their dynamics against the background of both treatment methods was analyzed every two weeks, the results of this analysis are shown in table 2.

**Table 2.** Cervical cytokine concentration and its dynamics in pregnant with CI

| Cytokine         | Group A                   | Group B                   | Group C     |
|------------------|---------------------------|---------------------------|-------------|
| Before treatment |                           |                           | 22 weeks    |
| N                | 47                        | 34                        | 30          |
| IL-6, pg/ml      | 1192±109,4 <sup>§</sup>   | 1234,2±202,9 <sup>§</sup> | 109,8± 13,3 |
| IL-8, pg/ml      | 25,5±3,2                  | 28,2±1,9                  | 28,6±3,9    |
| IL-10, pg/ml     | 135,6±34,2 <sup>§</sup>   | 123,5±28,7 <sup>§</sup>   | 267,7±36,7  |
| SLPI, µg/ml      | 1,8±0,2                   | 1,5 ±0,1                  | 1,0±0,3     |
| In 2 weeks       |                           |                           | 24 weeks    |
| N                | 46                        | 33                        | 30          |
| IL-6, pg/ml      | 1198,2±100,2 <sup>§</sup> | 1256,3±200,4 <sup>§</sup> | 203,7±23,1  |
| IL-8, pg/ml      | 28,4±3,51                 | 42,3±1,3                  | 29,9 ±3,3   |
| IL-10, pg/ml     | 139,5±14,9 <sup>§</sup>   | 129,2±21,2 <sup>§</sup>   | 204,1±43,3  |
| SLPI, µg/ml      | 1,9±0,4,                  | 1,0±0,1                   | 1,3±0,2     |
| In 4 weeks       |                           |                           | 26 weeks    |
| N                | 43                        | 30                        | 30          |
| IL-6, pg/ml      | 1187,4±102,4 <sup>§</sup> | 1224,6±109,3 <sup>§</sup> | 209, 8±12,9 |

Table 2 (continued)

| Cytocine     | Group A                    | Group B                    | Group C    |
|--------------|----------------------------|----------------------------|------------|
| IL-8, pg/ml  | 31,4±5,9                   | 68,2±6,7\$ <sup>#</sup>    | 27,5±6,7   |
| IL-10, pg/ml | 137,1±6,2 <sup>\$</sup>    | 128,8± 26,7 <sup>\$</sup>  | 200,6±27,9 |
| SLPI, µg/ml  | 3,7±0,9                    | 0,9 ±0,8 <sup>#</sup>      | 1,3±0,6    |
| In 6 weeks   |                            |                            | 28 weeks   |
| N            | 40                         | 24                         | 30         |
| IL-6, pg/ml  | 1203,6±109,7 <sup>\$</sup> | 1279,9±180,1 <sup>\$</sup> | 300,9±10,9 |
| IL-8, pg/ml  | 32,5±3,7                   | 187,6±25,0\$ <sup>#</sup>  | 29,9 ±5,0  |
| IL-10, pg/ml | 145,2±7,5 <sup>\$</sup>    | 130,4 ±21,7 <sup>\$</sup>  | 210,1±10,2 |
| SLPI, µg/ml  | 4,3±1,2                    | 0,6 ±0,2\$ <sup>#</sup>    | 1,4 ±0,8   |

\$ –  $p \leq 0,05$  comparing to group C

# –  $p \leq 0,05$  comparing to group A

Thus, before the use of the method of treatment, pregnant women with CI were distinguished from healthy pregnant women with the same gestational age only by a significant increase in IL-6 content (tenfold) and a slight increase in IL-10 (doubled) in cervical mucus. The rest of the investigated indicators of local immunity were similar in all groups.

Two weeks after the applied intervention, the general picture remains the same – high cervical concentrations of IL-6 do not undergo changes, in both groups being ten times more important than in healthy pregnant women (1198.2±pg/ml in group I, 1256.3 ± pg/ml in group B and 203.7 pg/ml in the group of healthy pregnant women). Instead, already at this stage, a tendency to increase the cervical content of IL-8 was determined in the obstetric pessary group (42.3 pg/ml versus 28.4 pg/ml in the cerclage group and 29.9 pg/ml in healthy pregnant women). The trend 2 weeks after applying the correction method has no statistical probability.

For 4 weeks after the correction of CI, a statistically significant increase in the cervical IL-8 content was found in the obstetric pessary group – 68.2 pg/ml when compared with the cerclage group – 31.4 pg/ml and 27.5 pg/ml in healthy pregnant women. However, already at this stage, we observe a tendency to decrease the content of SLPI in pregnant women with an obstetric pessary (1.9 µg/ml) and a simultaneous increase of this inhibitor in patients with a cerclage (3.7 µg/ml). These changes do not have a statistical probability,

however, in group A, the increase is the reaction of the mother's body to the active inflammatory process of the fetus, and the decrease in group B is the deficiency of this reaction against the background of local inflammation of the mother. A decrease in the content of SPLI in cervical mucus is considered one of the pathogenetic features of very early preterm labour.

For 6 weeks after the applied treatment, we observed an even greater increase in IL-8 in the cervical mucus against the background of the obstetric pessary, up to 187.6 pg/ml, in the cerclage group it remained the same as the indicator of the control group (32.5 pg/ml and 29.9 pg/ml respectively).

At the same time, 6 weeks after the intervention, changes in the cervical concentration of SLPI became statistically significant. In the cerclage group, where the increased content of IL-6 is persistently recorded, the value of SILP increases to 4.3µg/ml, and in the obstetric pessary group, against by the same high concentration of IL-6, it decreases to 0.6µg/ml.

A rapid increase in the cervical concentration of IL-8 within 4–6 weeks after the insertion of the obstetric pessary by more common phenomenon of bacterial vaginosis indicates an increase in the activity of the inflammatory process in the cervix, i.e., the risk of CI progression. IL-8 is of maternal origin, its activity is combined with the activity of IL-6 of fetal origin, which increases the risk of premature labor and rupture of fetal membranes.

## Discussion

The tendency to dominating of anaerobic microbiota in growth of pregnancy is more proper to obstetric pessary treatment, then cerclage. By the way, Xiao (2023) described alteration of vaginal microbiota by emergency cerclage as a decreasing of *Lactobacillus* abundance and an increasing of different pathogenic biotops.

This study demonstrated significant changes of vaginal microbiota by treatment of CI by pessary, but not by cerclage. Zhou X et al (2022) by investigation of vaginal microbiota of pregnant with twins an CI have found a significant decreasing of Ph and level of Lactobacteria and the increasing of *Gardnerella vag.* presence. They have also described a correlation between low meaning of vaginal Ph and negative neonatal outcomes. Danison (1999) have proved a role of SLPI lack in cervical ripening and maturing, and its depending on progesterone and IL-8.

The molecular changes of cervical mucus, investigated in this study, include significant increasing of SLPI by use of pessary, but not by cerclage (Park, 2023). Samejima (2021) demonstrated a correlation between this factor and other proinflammatory IL, and proved its role in cervix ripening by CI.

Diago Muñoz (2022) demonstrated a strong correlation between vaginal IL-6 concentration in vaginal secret and amniotic fluid in patients with CI, thus proposed a method of chorioamnionitis diagnostic without amniocentesis procedures. They noticed, that vaginal IL-6 concentration < 61.4 pg/ml is a good predictor of absence of chorioamnionitis, longer period to delivery and better neonatal results.

The changes of pro-inflammatory and anti-inflammatory factors balance, observed in this study, are parallel to changes of microbiota in pregnancy duration. Kindinger (2016) have proved, basing on observation of 687 pregnant with different types

of suture material, used for cerclage, the association between vaginal dysbiosis with inflammatory cytokine expression and interstitial collagenase activation in cervicovaginal fluid, leading to premature cervical remodeling. Seri (2023) proved a significant difference in pro-inflammatory markers concentration in cervical and vaginal secret in patients with CI comparing with healthy pregnant.

## Conclusions

1. There is a difference between the groups of cerclage and obstetric pessary in dynamic of microbiota changes – a tendency to increasing of laboratory criteria of bacterial vaginosis frequency in group of obstetric pessary in 2 weeks becomes significant in 4 and more in 6 weeks comparing with group of cerclage.

2. Proper to cervical insufficiency high concentration of proinflammatory IL-6 and IL-10 by use of obstetrical pessary is complicated by increasing of IL-8 and decreasing of SLPI, what means an activation of cervical inflammation, by cerclage – an increasing of SLPI is observed, what is favourable for pregnancy.

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## Conflict of interests

All authors declare the absence of conflict of interests

## Consent to publication

All authors have got consent to publication of this article.

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## Локальні запальні чинники у вагітних з різними методами лікування істміко-цервікальної недостатності

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**Анотація:** причинами формування цервікальної недостатності вважають порушення співвідношення елементів сполучної тканини внаслідок її генетичних особливостей, гормональний дисбаланс та переважання прозапальних факторів імунної системи. Особливу увагу приділено клінічним ситуаціям, коли цервікальну недостатність діагностовано в терміні 22-24 тижні, лікування тут має на увазі альтернативу екстреного серкляжу та акушерського пессарію. Мета дослідження – порівняти динаміку вагінальної мікробіоти та місцевих факторів цервікального імунітету за допомогою різних методів лікування цервікальної недостатності. Матеріали та методи. Перебували під спостереженням 81 вагітна з недостатністю шийки матки, діагностованою в терміні 22-24 тижні, 47 вагітних лікувались методом серкляжу (група А), 34 вагітним був встановлений акушерський пессарій (група Б). Групу С склали 30 здорових вагітних у терміні 22 тижні. Усім пацієнткам до початку лікування та кожні два тижні після нього проводили мікроскопію вагінальних виділень за критеріями Хей-Айсон та визначення вмісту цитокінів в цервікальному слизі. Результати. Співвідношення I та III типу мазку за критеріями Хей-Айсон, будучи подібним до лікування, за використанням акушерського пессарію з пролонгуванням вагітності, різко змінюється на поширеність бактеріального вагінозу – з 30,3% до 21,2% у 2 тижні до 25,0% і 41,7% за 6 тижнів, серкляжем – від 43,5% і 14,9% за 2 тижні до 30,3% і 17,5% за 6 тижнів. У пацієнток із цервікальною недостатністю підвищена концентрація IL-6 та IL-10, але при використанні акушерського пессарію додатково реєструється зростання IL-8 з 42,3 пг/мл через 2 тижні до 187,6 пг/мл через 6 тижнів, а також зниження SLPI з 1,5 мкг/мл до 0,6 мкг/мл. Обидві зміни свідчать про прогресування запалення та пов'язані з негативними результатами вагітності. При цьому серкляж асоціюється зі зростанням SLPI від 1,9 мкг/мл до 4,3 мкг/мл, що є маркером адекватної імунної реакції на вагітність. Існує різниця між групами серкляжу та акушерського пессарію в динаміці змін мікробіоти – тенденція до підвищення лабораторного критерію частоти бактеріального вагінозу в групі акушерського пессарію через 2 тижні стає достовірною через 4 і більше через 6 тижнів порівняно з групою акушерських пессаріїв. серкляж. Властиві цервікальній недостатності висока концентрація прозапальних IL-6 та IL-10 при використанні акушерського пессарію ускладнюється підвищенням IL-8 і зниженням SLPI, що означає активацію запалення шийки матки, при серкляжі – спостерігається підвищення SLPI, що сприятливо для вагітності.

**Ключові слова:** інгібітор секреторної лейкоцитарної пептидази, інтерлейкін-6, інтерлейкін-8, інтерлейкін-10, бактеріальний вагіноз, лактобактерії.



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