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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE ROLE OF LAPAROSCOPIC CERCOLOGY AND CYTOKINES IN CERVICAL MUCUS IN THE PREVENTION OF ANTENATAL LOSSES

Specialty: 3215.01 - Obstetrics and gynecology

Field of science: Medicine

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GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and development degree. One of the priorities of the successful social policy of Azerbaijan Republic is the prevention of maternal and child health and all kinds of reproductive losses. The quality of antenatal care during pregnancy must be sufficiently high to ensure that the outcome is favorable and positive for the mother, fetus, and newborn[1;2;3]. The organization of perinatal care is analyzed by the relevant structures of the Ministry of Health of Azerbaijan as a medical-social and medical-demographic issue. For this reason, one of the key criteria in the prevention of reproductive losses is the prognosis of pregnancy progression and the study of its outcomes. Reproductive losses, especially disruption of pregnancy in the II trimester, remain an actual problem in modern obstetrics. Despite the use of a complex of various diagnostic and treatment methods, the frequency of fetal loss is 10-25% according to various indicators, and this indicator remains at a fairly high level. Violation of the physiological mechanisms of gestation during pregnancy lays the groundwork for the development of obstetric complications, and is considered a risk factor for childbirth with a pathological course and the postpartum period[4]. Complex factors affect the development of disorders: medical-biological factors, chronic extragenital diseases, patient follow-up tactics and

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[1] Воронцова М.С. Способ ведения беременных с истмико-цервикальной недостаточностью / М.С. Воронцова, Е.Н. Кравченко, О.Ю. Цыганкова // Мать и дитя в Кузбассе. – 2018. – № 1. – С. 39-44.

[2] Сазонова, Н.Г. Методики протеомного анализа и их роль в диагностике акушерской и гинекологической патологии / Н.Г.Сазонова, Т.А.Макаренко, Р.Я.Оловянникова [и др.] // - Москва: Журнал акушерства и женских болезней. - 2019. - Т.68. - №1. - с.69-82.

[3] Jarde, A. Vaginal progesterone, oral progesterone, 17-OHPC, cerclage, and pessary for preventing preterm birth in atrisk singleton pregnancies: an updated systematic review and network metaanalysis./ A.Jarde, O.Lutsiv, J. Beyene // SD BJOG . – 2019. - №.2, p.126- 156.

[4] Chatzakis, C. Emergency cerclage in singleton pregnancies with painless cervical dilatation: A meta-analysis. / C.Chatzakis, A.Efthymiou, A.Sotiriadis [et al.]

// Acta Obstet. Gynecol. Scand.- 2020. - №.9. – p.1444–1457.

pharmacological therapy of pregnancy are considered more important.[5;6] Antenatal infection is considered to be one of the main causes of spontaneous abortion in the II trimester, premature births, and the difficult course of the postpartum period for the mother and the fetus. Infectious agents include a wide range of agents: along with pathogenic agents, the role of conditionally pathogenic microflora has also been proven. According to many researchers, miscarriages of unknown etiology make up from 7% to 50% of reproductive losses. In more than half of the patients, it is recorded that these or other reasons are present together. Complex social conditions, difficult family circumstances, early initiation of sexual life, the spread of sexually transmitted infections, as well as the increase in the number of pregnancies among women of advanced reproductive age, bring this problem to the forefront.[7;8] Despite the relevance of preventing complications related to the second trimester and the risk of miscarriages, this issue remains under-researched. The II trimester is considered the most important period of gestation. During this period of gestation, certain hormonal-metabolic changes occur in the orgasm of the future mother. Increasing circulatory and hypoxic disturbances in the II trimester of gestation, lead to the deepening of the primary pair deficiency and the secondary wave of trophoblast invasion in the vascular walls of the myometrial segment, damaging to the vascular ring of the placental barrier, and spasm of arterial and capillary sphincters.

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[5] Тютюнник, В. Л. Вагинальные инфекции как фактор риска преждевременных родов // - Москва: Эффективная фармакотерапия. – 2017. – № 10. – с. 20-23.

[6]Bianchi-Jassir, F. Preterm Birth Associated With Group B Streptococcus Maternal Colonization Worldwide: Systematic Review and Meta-analyses. / F.Bianchi-Jassir, A.C.Seale, M.Kohli-Lynch // Clin Infect Dis.-2017,- № 6.- p.133-142.

[7] Jarde A. Combining Interventions to Prevent Preterm Birth in Women at Risk: a Systematic Review and Meta-Analysis // J. Obstet. Gynaecol. Can. – 2017. – Vol. 39, № 12. – p. 1192-1202.

[8] Baños, N. Mid-Trimester Cervical Consistency Index and Cervical Length to Predict Spontaneous Preterm Birth in a High-Risk Population // AJP Rep. – 2018. – № 8. – p.43-50

There are also two crisis periods in the development of the fetus - 15-20 weeks (intensive growth of the brain) and 20-24 weeks – the formation of the main functional systems.[9;10]

Preterm births (PB) are considered a serious medical and social problem due to the high rate of perinatal mortality among prematurely born infants. High rates of perinatal mortality make PB a significant medical and social issue. Perinatal and infant mortality rates are particularly high in premature infants. For instance, up to 50% of cases involving extremely low birth weight (ELBW) are associated with severe disabilities such as cerebral palsy (CP), hearing or vision loss, and cognitive developmental disorders. Thus, conducting research aimed at studying the pathogenesis of spontaneous preterm births (PB) enables the development of preconception care, strategies for PB prevention, and the establishment of a management algorithm for pregnant women at high risk of PTB[11];[12]. It also facilitates the investigation of perinatal morbidity and mortality during preterm deliveries and the formulation of optimal delivery tactics.

One of the ways to reduce the frequency of premature births is the timely detection of the threat of miscarriage (TOM) and elimination of symptoms. The researches devoted to this problem were mainly carried out from the 18-19th week of pregnancy to the 23rd week, when, according to the data of transvaginal cervicometry,

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[9]Krispin, E. Primary, secondary, and tertiary preventions of preterm birth with cervical cerclage. / E.Krispin, S.Danieli-Grube, E.Hadar [et al.] // Arch Gynecol Obstet . – 2019. - №12. – p.300-305.

[10]Davidesko, S. Long-Term Infectious Morbidity of Premature Infants: Is There a Critical Threshold? / S.Davidesko,T. Wainstock, E.Sheiner [et al.] // J. Clin. Med. -2020. - №.9. – p.30-38.

[11] Magalov, I. Laparoscopic approach for surgical correction of obstetric complications in postpartum / I.Magalov, A.Poluxova, A.Aliyeva // Abstracts of the 26th Annual Congress of the European Society for Gynaecological Endoscopy (ESGE) 18th – 21st October 2017, Turkey, p.26-39.

[12] Pinheiro Filho, T.R. Risk assessment for preterm delivery using the fetal fibronectin test associated with the measurement of uterine cervix length in symptomatic pregnant women. / T.R.Pinheiro Filho, V.R. Pessoa, T.S.Lima [et al.] // RevBrasGinecolObstet. - 2018. - №6.- p.507–512.

attention should be paid to the shortening of the length of the cervix.[13;14] Traditionally, lower abdominal pain is considered as one of the main symptoms of PB. Therefore, in order to prevent overdiagnosis and unwarranted hospitalization, lower abdominal pain should not be overlooked, as it may sometimes be related to bowel dysfunction or physiological stretching of the uterine ligaments, even in the absence of cervical changes. This creates the need to use the concept of "real" danger of pregnancy disruption. There is no doubt that the most important diagnostic criterion for assessing the 'true' risk of preterm birth (PB) is the cervical length measured by transvaginal ultrasonography.[15;16]

At present, studies have been conducted to study the characteristics of the production of autoantibodies during endometriosis and related infertility. It has been established for quite a long time that the amount of anti-endometrial antibodies, as well as autoantibodies against phospholipids, annexin, laminin, is increased both in blood serum and peritoneal fluid of patients with endometriosis. However, until now there is no consensus on their role in the pathogenesis of this pathology. Scientific studies dedicated to the study of the characteristics of B-lymphocyte differentiation and activation during infertility caused by various degrees of widespread endometriosis have not been carried out before.

One of the effective methods for reducing reproductive losses is the targeted prevention of obstetric complications by identifying

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[13]Алехина А.Г. Невынашивание беременности вследствие истмико-цервикальной недостаточност / А. Г. Алехина, А. Е. Блесманович, Ю. А. Петров // - Москва: Синергия Наук. – 2018. – № 19. – с. 990-998.

[14]Owens, D.K. Screening for Bacterial Vaginosis in Pregnant Persons to Prevent Preterm Delivery: US Preventive Services Task Force Recommendation Statement. / D.K.Owens, K.W.Davidson, A.H.Krist // JAMA. – 2020. - №7.- p.1286-1292.

[15]Белоусова, В.С. Преждевременные роды: от понимания патогенеза к тактике ведения. / В.С. Белоусова, А.Н. Стрижаков, Е.В. Тимохина [и др.] // - Москва: Акушерство, гинекология и репродукция. -2018 -Т.12 -№ 4.- с. 47-51.

[16]Kimber-Trojnar Z. Management of concomitant cervical insufficiency and intrauterine adhesions. //Ann. Transl. Med.- 2020. - № 8. – p.526- 528.

perinatal risk factors. Currently, it is indisputable that the preconception phase, transitioning from preventive care in the first half of pregnancy to treatment in the second half, follows the principles of perinatal risk strategy. However, the scientific basis for selecting women at risk of pregnancy complications during the antenatal period has not been fully established, and comprehensive therapeutic, preventive, and prognostic measures have yet to be developed.

The objective subject of the research. Between 2018 and 2022, a prospective study of 101 patients was conducted to determine the impact of the risk of second-trimester pregnancy complications on the course of pregnancy and delivery. The age range of the women was between 22 and 35 years, with a mean age of 28.7±4.06 years. The main group of patients was divided into two subgroups: the first group included 46 women at risk of miscarriage between 12 and 21 weeks of gestation, and the second group included 55 women at risk of preterm birth between 22 and 28 weeks of gestation. The control group consisted of 25 women with a physiological course of pregnancy.

The purpose of the study. There was a study of the role of laparoscopic cerclage and cytokines in cervical mucus in the prevention of antenatal losses in the second trimester of pregnancy.

The main tasks of the research:

1. Prospective and clinical-laboratory examination of women at risk of miscarriage in the II trimester of pregnancy;
2. To determine the need for antenatal prophylactic measures, it is essential to study the risk factors associated with pregnancy complications;
3. Development of the optimal antenatal diagnostic-treatment algorithm in the second trimester of pregnancy;
4. Study of labor activity and perinatal outcomes in women who are at the risk of miscarriage in the antenatal period;
5. In addition to the comparative analysis of complex therapeutic and prophylactic measures for pregnancy complications in the second trimester, it is essential to evaluate their quality.

Research methods. In the conducted complex studies, a number of modern examination methods, including: clinical-laboratory, instrumental, bacteriological, immunological, statistical, etc. methods were used.

The main provisions of the dissertation defended:

1. The implementation of active tactics of follow-up of patients with TOM significantly improves obstetric and perinatal prognosis, helps to maintain pregnancy for a longer period of time, reduces the frequency of very early births, perinatal losses and neonatal morbidity and allows patients to reduce the duration of hospitalization in the second stage of care.
2. In order to reduce the frequency of PB, it is appropriate to detect the danger of "real" disruption of pregnancy and isthmic-cervical insufficiency from the beginning of the second trimester.
3. Complex assessment of the main pathogenetic mechanisms of spontaneous PB allowed to develop a pathogenetically based algorithm of pre-gravid preparation, pregnancy prevention and follow-up in women belonging to the PB risk group.

Research innovation:

1. For the first time in Azerbaijan, the characteristics of anamnestic and clinical indicators when the danger of miscarriage occurs in the II trimester of pregnancy were revealed, and ideas were obtained about the pathogenesis of miscarriages and pregnancy disorders in the II trimester.
2. It has been established that preterm births are of inflammatory origin, as high concentrations of inflammatory cytokines and TNF-α have been detected in the myometrium, amniotic fluid, cervical mucus, and umbilical cord blood during preterm labor.
3. Laparoscopic cerclage is performed only when access through the uterus is technically impossible, which occurs due to the absence of the uterine part of the cervix or after unsuccessful attempts at cervical cerclage. Cervical cerclage or placing stitches on the cervix is a surgical procedure that is important for maintaining closing function during pregnancy.

4. Complex study of the links of the pathogenesis risk of miscarriage allowed to develop a pathogenetically based approach to gravid-preparation, prevention and follow-up of pregnancy in women from the risk group.

Theoretical and practical significance of the research. In order to detect isthmic-cervical insufficiency in time, the assessment of the condition of the cervix should be started from the 14-16th week (especially in high-risk groups). Among the markers of premature births, the study of the amount of TNF-α, IL-2, IL-4, IL-6, IL-10 in the contents of the uterus made it possible to identify pregnant women with neonatal infection and predict the occurrence of births earlier than 34 weeks of gestation. It is important to perform laparoscopic cerclage in the pre-gravid stage and from 10-11 weeks to 15-16 weeks of pregnancy in women who are at risk of premature births. The understanding of the main links of the pathogenesis of spontaneous preterm births in practical healthcare has allowed the development and application of a pathogenetic-based algorithm of gravid preparation, pregnancy prevention and follow-up in women from the risk group of PB, as well as the justification of tocolytic therapy and optimal delivery tactics during spontaneous preterm births, which has made it possible to reduce the frequency of PB (especially extremely early or only early), the frequency of perinatal morbidity and mortality, as well as to improve the long-term outcomes of PB. Application of this algorithm made it possible to reduce the frequency of premature births by 8.6 times, extreme early and only early births to 0%, perinatal morbidity by 8.6 times, and perinatal death to 0%.

Research approval and application of results. Based on the materials of the dissertation, a scientific-practical conference dedicated to the birthday of Aziz Mammad Karim oglu Aliyev was held in Baku in 2020, as well as the 'Modern Achievements of Azerbaijani Medicine' scientific-practical conference in Baku in 2017. The initial discussion of the dissertation was presented and discussed at the meeting of the Department of Obstetrics and Gynecology of the Azerbaijan State Institute for Advanced Training of Doctors named after A.Aliyev (Protocol No.08, dated 16.04 2024),

at the Scientific Seminar under the Dissertation Council ED2.6 operating under the Azerbaijan Medical University (Protokol No.13, dated 27.06.2024).

7 journal articles and 3 theses were published on the basis of research conducted on the topic of the dissertation, 3 of which were published abroad (on the list of AAK and Scopus indexing database).

The materials of the dissertation are used in the teaching process of the Department of Obstetrics and Gynecology of ASATID named after A. Aliyev, the proposed practical recommendations are applied to practice in the Department of Obstetrics and Gynecology "Leyla Medical Center".

The name of the institution where the dissertation work was performed. Department of Obstetrics and Gynecology, "Leyla Medical Center", Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev.

The structure and scope of the dissertation.

The dissertation is printed on 175 pages (218,099 characters) and consists of the following sections: 'Table of Contents,' 'Introduction' (7 pages, volume: 12,470 characters), 'Results' (3 pages, volume: 4,584 characters), 'Practical Recommendations' (1 page, volume: 748 characters), and 'List of References' (24 pages). The main content of the dissertation is divided into six chapters. Chapter I is 'Literature Review' (27 pages, volume: 54,027 characters), Chapter II is 'Materials and Methods' (13 pages, volume: 21,391 characters), Chapter III is 'Research Results' (27 pages, volume: 36,223 characters), Chapter IV (25 pages, volume: 30,074 characters), Chapter V (26 pages, volume: 29,532 characters), and Chapter VI is 'Discussion of Results' (15 pages, volume: 29,050 characters). In total, 204 sources were referenced in the dissertation, including 15 Azerbaijani, 73 Russian, and 116 works by foreign scholars. The dissertation includes 29 tables, 12 photographs, and 27 graphs.

RESEARCH MATERIAL AND EXAMINATION METHODS

The dissertation work was conducted within the scientific program of the Department of Obstetrics and Gynecology at the Azerbaijan State Institute for Advanced Medical Studies named after E. Aliyev from 2018 to 2022. The examinations were carried out using a prospective method at the clinical bases of the Department of Obstetrics and Gynecology at the Azerbaijan State Institute for Advanced Medical Studies and the 'Leyla Medical Center' Obstetrics and Gynecology Department. To determine the impact of the risk of pregnancy complications during the second trimester on pregnancy outcomes and delivery, a prospective study was conducted involving 101 patients at risk of pregnancy complications. The age limit of women was between 22-35 years old, the average age limit was 28.7±4.06 years. Patients in the main group are divided into 2 subgroups:

Group 1 included 46 women at the risk of miscarriage in the 12-21 weeks of pregnancy.

Group 2 included 55 women at the risk of premature birth in the 22-28th week of pregnancy.

The control group included 25 women with a physiological course of pregnancy, aged between 21 and 35 years, with a mean age of 27.8 ± 2.11 years (Table 1).

Table1 1. Age of patients in comparison groups

Age, year	I group (n=46)		II group (n=55)		Control group (n=25)	
	Abs.	%	Abs.	%	Abs.	%
22- 25	12	26,1±6,5	16	29,1±6,1	10	40,0±9,7
26-30	18	39,1±7,3	20	36,4±6,6	8	32,0±9,3
31-35	16	34,8±6,8	19	34,5±6,4	7	28,0±8,9

A comprehensive approach utilizing various examination methods was employed in the dissertation work:

1. **Anamnestic examination method:** The somatic and obstetric-gynecological histories of the patients were studied.
2. clinical, laboratory and instrumental examination methods.

All patients underwent general clinical examinations, ultrasound and dopplerometry of veins in the fetoplacental complex, evaluation of uterine contraction activity using a fetal monitor at the obstetrics and gynecology department of "Leyla Medical Center" in addition to general clinical examinations (blood group and Rhesus factor, complete blood count, RW, HbsAg, HIV-screening of blood, microflora examination of the reproductive tract, bacterial smear from the child's throat, PCR-sputum smear), biochemical examination methods (coagulogram, complete blood count, carbon dioxide, urea, creatinine, liver tests, transaminase of the thyroid gland), additional methods of small thyroid blood cells , ECG, hysteroscopy, histological examination), specific examination methods (level of blood cytokines, interleukin-1b (Il-1b), Il-6, tumor necrosis factor (TNF), expression of TRL 2, TRL 4 in blood serum) were applied. The amount of anti-inflammatory cytokines (SNA-α, IL-2, IL-6) and anti-inflammatory cytokines (IL-4, IL-10) in the mucus taken from the cervical canal was determined.

Echographic examinations were performed with the help of ultrasound diagnostic devices "General Electric, Voluson E8" (made in the USA, 2010). When the diagnosis of isthmic-cervical insufficiency (IS) was confirmed, the issue of choosing a correction method was resolved as follows: vaginal or transabdominal (laparoscopic) by surgical correction or by placing an obstetric pessary.

Statistical software "Statistics for Windows" v.6.1, Stat-Soft Inc. (USA) was used for statistical processing of the obtained data. The statistical analysis of the obtained data was carried out depending on the type of the sign and its distribution, and at this time, the average values and their errors were calculated, and the accuracy of the differences was determined according to the Student's t test.

RESULTS OF PERSONAL OBSERVATIONS AND THEIR DISCUSSION

The analysis of the conducted gynecological pathology has shown that the patients in the main group have more frequent inflammatory diseases of the reproductive system organs than the control group. It should be noted that in the structure of inflammatory diseases of women in the main group, the specific weight of non-specific colitis was the highest and it was found in 45.6% in group I and 43.6% in group II. In the last decade, disturbances in the microecology of the uterus are considered to be one of the frequently mentioned complications of pregnancy. Endocervicitis was detected in every third patient in all examined groups and it's frequency was 32.6% in group I and 30.9% in group II. Chronic salpingo-oophoritis was detected in 12.0% of women in the control group, 36.9% in group I and 23.6% in group II. No honest differences were found for other remaining diseases, which play a major role in situations related to functional changes of the reproductive system. Thus, prognostically important gynecological diseases associated with the development of TOM in the II trimester of pregnancy: inflammatory diseases of small pelvic organs, endocervitis, chronic salpingophoritis, ovarian cysts, non-specific colitis were found. Non-specific infectious diseases of the uterus are represented as one of the leading risk factors in the formation of TOM in the II trimester. Pregnant women with past inflammatory diseases of small pelvic organs, dyshormonal diseases (myoma, endometriosis, ovarian cysts) should be included in the risk group for the development of pregnancy disruption in the II trimester of pregnancy. In all pregnant women with non-specific vaginitis, it is necessary to carry out rehabilitation of the uterus with complex preparations that affect anaerobic, aerobic flora and candida (along with controlling the level of recovery and restoring the necessary amount of lactobacilli).

Analysis of the conducted somatic pathology showed that the majority of women in both groups often suffered from inflammatory diseases. In our study, 12 (26.1%) patients in group I and 7 (12.7%) patients in group II had a history of frequent acute respiratory viral infections (ARVI). At this time, 28.0% of women in the control group had a history of acute respiratory viral diseases. In the

anamnesis, tonsillitis was recorded in 5 women (10.9%) in Group I and in 8 women (14.5%) in Group II, while chronic sinusitis was noted in 2 women (4.3%) in Group I and in 3 women (5.5%) in Group II. Chronic bronchitis was found quite often, as it was found in 8.0% of patients in the control group, -17.3% in group I and -7.3% in group II. Among the examined groups, the detection of urinary tract infections in women attracts attention: pyelonephritis 2 (4.3%) in group I and 3 (5.5%) in group II, chronic cystitis 3 (6.5%) in group I, II in 2 (3.6%) women in the group. In addition, chronic gastritis (in the control group - 8.0%, in group I - 6.5%, in group II - 9.1%) was found among diseases of the gastrointestinal tract. Extra genital pathologies mentioned by many researchers have been considered as a risk factor of reproductive losses. Obesity, which is the result of the development of metabolic disorders and impaired glucose tolerance is of particular interest.

Thus, obesity was detected in 6 (13.0%) patients in group I, 12.7% (7) in group II, and 3 (12.0%) patients in control group. Body weight deficiency was more commonly observed in patients with complicated pregnancies, recorded in 8.9% of Group I and 7.3% of Group II. Dysmenorrhea was found in 8.8% of examined women in group I, 10.9% in group II, and 12.0% of women in control group at the time of inclusion in the study in patients with TOM. Hyperpolymenorrhea was found in 13.0% of examined women in group I, 9.0% in group II and 12.0% in control group. Irregular menstruation was recorded in 15.2%, 23.7% and 8.0% of women, respectively. Anamnesis data on previous pregnancies were also analyzed. One fact is particularly noteworthy that 39.1% of women in group I, 29.1% of women in group II and 24.0% of women in the control group became pregnant for the first time. At this time, 45.6% of women in group I and 27.2% of women in group II had a history of complicated miscarriage. 15.2% of patients in group I, 16.4% in group II have abortions in their anamnesis. Thus, examination data of women in comparable groups confirm that inflammatory diseases of the organs of the reproductive system are quite common in the anamnesis of patients suffering from TOM. There were no significant differences in other gynecological and somatic pathologies in the groups.

General clinical examination, ultrasound scanning and dopplerомtry of the vessels of the fetoplacental complex, evaluation of uterine cotraction activity with the help of a fetal monitor were performed on all patients in the maternity hospital. The dopplerometric examination of the blood flow in the uterine arteries was carried out from the 21st-22nd week of gestation. Systolic-diastolic ratio (SDR), pulsatility index (PI) and resistance index (RI) were determined.

In the patients of the main group, the width of the cervical canal was 11.6±0.5 mm on average, which was 41.5% more than the control value (control - 8.2±0.4 mm). According to the data of USM, pregnant women in the main group had 18.0% shortening of the length of the cervix (UBU) from the 20th to the 28th week of gestation. In the main group, 86 (85.1%) pregnant women had uterine-pair blood flow disorders. SDN, RI and PI were at the level of the upper limit of the control indicator in 15 other women with a risk of pregnancy loss. Thus, the range of SDN price change is 1.76-2.03 in the control group, 2.02-2.78 in the main group, RI - 0.44-0.58 and 0.55-0, respectively. 88, PI was -0.92-1.10 and 1.10-1.30. At this time, uterine blood circulation disorders were found in all 49 (48.5%) patients with double deficiency, 22 (21.8%) women with exacerbation of genital infections, and 15 (14.8%) women with gestational pyelonephritis. From the presented data, it can be seen that the reduction of SDN and RI was more noticeable in the main group. Thus, the difference between the average value of SDN in the 21-22 weeks and 27-28 weeks is 0.18 conditional units (control - 0.07), RI 0.18 conditional units (control - 0.06) organized. The performed examinations showed that the hemodynamic disturbances occurring in the uterine artery in the majority of patients were detected in the period of 27-28 weeks.

Using standard media for gram-positive and gram-negative microorganisms, cultural examination of cervical canal secretions and urine was carried out, diagnostics of sexually transmitted infections (STIs) by PCR and IFA methods, examination of uterine secretions by PCR method, real-time detection of results and "Femoflor" with the help of the system, conditionally pathogenic micro-organisms and Lactobacillus spp. **Among the patients in the main group, the following infections were identified:** candidiasis

in 46.5%, bacterial infections in 15.8%, ureaplasmosis in 14.8%, trichomoniasis in 13.9%, herpes simplex virus in 11.9%, chlamydia in 8.9%, and mycoplasmosis in 5.9%. The coccal flora, Leptotrichia spp. and Candida spp. found only in patients in the main group. Among the infected women, monoinfection in the form of candidiasis was recorded in 3 persons, trichomoniasis in 2 persons, chlamydiosis in 1 person. When there are associations of 2 microorganisms, bacterial flora - intestinal bacilli, staphylococcal, streptococcal, and enterococcal infections were prevailed.

During the study of current pregnancy characteristics in women with TOM, it was found that the patients complained of pain in the lower abdomen or back, the tone of the uterus did not increase, according to the data obtained during the examination of the last uterus, according to the indicators of the fetal monitor during the normal length of the cervix. In group I, 16 women (34.8 ± 7.0%) reported painful sensations in the lower abdomen and lower back, while 23 women (50.0 ± 7.3%) reported no complaints. In group I, 7 women (15.2 ± 5.3%) complained of cramping-type pains, compared to 14 women (25.5 ± 5.9%, p = 0.0001) in group II. In group I, 23 patients (50.0 ± 7.3%) did not report any pain, whereas nearly all women in group II reported some form of complaint (p = 0.001). Regarding lower abdominal and lumbar pain, 16 pregnant women (34.8 ± 7.0%) in group I and 39 women (70.9 ± 6.1%) in group II reported such complaints (p = 0.0001). The incidence of cramping-type pain was reported by 7 individuals (15.2 ± 5.3%) in group I and 14 individuals (25.5 ± 5.9%) in group II (p = 0.0001). According to our data, the incidence of ISI develops in 27.5 ± 4.5% of examined women starting from the 18th week of gestation (Table 2).

Table 2. Timing of the detection of HPT and ISI during the second trimester

Duration of gestation (weeks)	IeH (n=66)		ISI (n=35)		χ^2	p
	absolute	%	absolute	%		
22-23	18	27,3±5,5	12	34,3±8,0	1,28	>0,05
24-25	21	31,8±5,7	14	40,0±8,3	0,24	>0,05
26-28	27	40,9±6,0	9	25,9±7,4	0,78	>0,05

According to the cervicometry data, the average length of the cervix was 22.8±1.6 mm in group I and 32.4±2.2 mm in group II. Among the patients in group I, the shortest length of the cervix was 18.6 mm, the longest was 25.3 mm. Of the 46 pregnant women, 21 (46.3 ± 7.3%) also exhibited dilation of the cervical internal os greater than 5 mm. In the study's Group II, the cervical length ranged from a minimum of 24.1 mm to a maximum of 42.2 mm. In Group II, among the women with cervical dilation (14, 25.5 ± 5.9%), the cervical lengths measured 24.1 mm, 25 mm, 25.5 mm, and 25.9 mm, compared to Group I ($\chi^2 = 42.21$, $p = 0.001$). Thus, it can be noted that 46.3±7.3% of 46 women with a short cervix were diagnosed with UTI. Among women with normal cervical measurements, only 25.5 ± 5.9% of pregnant women exhibited dilation of the internal os.

According to the data of the general examination of blood conducted in most of the patients, the blood indicators in both group I and group II were within the normal range. Grade I anemia was found in 14 (30.43%) patients in group I and 29.09% in group II. In general, the presence of a defined level of TNF in the blood was associated with a fair risk of pregnancy failure; determination of cytokine in the range of 0-43.6 pg/ml was associated with an increased risk of pregnancy failure. As in the case of SNA, IL-1b values higher than the median value were 4 times more common in the main group. No significant differences were found in the studied groups in the studies conducted to determine TLR2 expression. In our study, we could not observe significant differences in the relative amount of TLR4 in peripheral blood leukocytes, but the analysis of values higher than the median values for all patients included in the study (baseline and control group) showed that the absence of TOM was associated with their honestly low frequency (32.5% and 74.0%, respectively, $p<0.001$). Thus, the applied special examination methods show that determination of TLR2 expression in the blood serum of pregnant women does not have honest differences during the physiological and complicated course of pregnancy. The TLR4 study data revealed some differences in the comparison groups. During the physiological course of pregnancy, the expression of TLR4 in the blood of a pregnant woman was not higher than 0.10%,

the values of this indicator above 0.14% are characteristic for the danger of pregnancy disruption has been associated with an increased risk of miscarriage.

In pregnant women in the main group and pregnant women in the control group, there are honest differences in the amount of cytokines in the contents of the cervical canal in the first trimester: in the main group, the levels of both pro-inflammatory and anti-inflammatory cytokines were 2 times and higher than in the control group. The analysis of changes in the amount of cytokines in the mucus of the cervical canal in patients in the control group showed that in the first trimester of pregnancy practically all studied cytokines were characterized by quantitatively minimal values. The amounts of cytokines in the cervical mucus of pregnant women at various gestational durations are presented in Table 3.

Table 3. Levels of cytokines in the cervical canal secretions of examined pregnant women (pg/ml)"

Cytokine	Trimester of pregnancy	Control group (n=25)	Main group (n=101)
TNF-a	I	15,8±3,5	54,5±5,4*
	II	12,4±3,3	43,8±5,6
	III	16,4±3,2	63,2±7,5
İL-2	I	5,3±2,3	24,0±3,7*
	II	5,2±2,1	18,5±3,2*,**
	III	4,1±1,2	32,6±4,2 **
İL-4	I	2,6±1,2	42,7±5,4*
	II	3,2±1,7	31,2±4,3**
	III	4,5±1,8	56,1±5,6**
İL-6	I	7,6±2,7	57,2±5,2*
	II	3,5±1,5	48,8±5,3*,**
	III	6,8±2,8	72,7±6,8 *,**
İL-10	I	23,7±3,3	68,3±6,6 *
	II	19,5±3,4	53,7±5,2**
	III	29,6±3,8	91,8±6,5

Note: *The mean values of the indicator were significantly different between groups at the same gestational durations ($p < 0.05$); ** The mean values in the second and third trimesters were significantly different from those in the first trimester within the specified groups ($p < 0.05$).

Then, in the absence of honest differences, different trends are revealed the changes in the amount of cytokines studied in the following trimesters (with the exception of IL-10, it's level honestly increases in the III trimester compared to its level in the I trimester). In the dynamics of pregnancy in women of the main group is probably due to the absence of acute inflammation of the uterine mucosa during the termination of pregnancy. Nevertheless, it is clear that local immune reactions during normomicrocinosis of the uterus tend to maintain a constant concentration of secreted cytokines throughout pregnancy. During the examination of women in the II and III trimesters of pregnancy, there were no honest differences in the amount of cytokines between the groups. IL-6 and IL-2 were exceptions. It should be noted that according to the data of the microbiological examination, the microflora of the uterus in pregnant women in the main group after treatment corresponded to the indicators in healthy pregnant women and decrease in the level of many cytokines (with the exception of the level of HNA-). In order to reveal the risk factors of the threat of premature termination of pregnancy (PTOP), we studied the anamnesis, the data of extragenital and gynecological diseases, as well as the complications of pregnancy in patients with "true" TOM (group I, n=66) and ICH (group II, n=35), and compared with those examined in the control group. The obtained data show that the frequency of pregnancy after ECF in women observed in groups I and II is significantly higher than in the control group ($p<0.05$). TOM is more specific for women who have given birth for the first time, but at the same time, the frequency of development of SCI is not related to parity. Some factors like spontaneous and artificial abortions, correlation dependence is observed between pregnancy failures in the anamnesis. Thus, 13 out of 66 patients in group I (19.69±4.9%) and 6 out of 35 examined women in group II (17.14±6.3%) had a history of preterm labor (PL). In recent years, the significance of the problem of early and very early PL related to ICU for obstetricians has increased many times due to the registration of perinatal death from the 22nd week of gestation according to the new criteria of live birth. Research aimed at optimizing obstetrical tactics during ICH allows to

reduce the level of early neonatal death (ND) and perinatal death (PD), as well as the level of morbidity of newborns, and to reduce the share of financial costs incurred for the rehabilitation and treatment of premature children.

The high frequency of PB and perinatal losses associated with UTI, the lack of generally accepted follow-up tactics of pregnant women, creates the need to optimize the tactics of patients follow-up with UTI. The risk factors of SCI are described in detail in the scientific literature, but the individual risks (which can be calculated at the stage of pregnancy planning) are not given due attention. Therefore, it is necessary to study individual risk factors and carry out its timely and adequate prevention at the stage of pre-gravid preparation, which determined the relevance of the current research work. The most common complication of pregnancy in patients with both "true" TOM and ICU was TOM in the first trimester, and it was 34.84±5.9% and 28.57±7.6%, respectively, in those examined in groups I and II.

In our study, bloody secretions in the first trimester were equally recorded in both groups I and II. In the absence of bloody secretions, hematomas were detected in 16 of 66 (24.24±5.3%) and 5 of 35 (14.28±6.0%) examined women (χ^2=0.45, p> 0.05), which can be considered as a risk factor for early pregnancy loss (TOM) in the second trimester. During the objective examination of the patients with "true" TOM upon admission to the hospital, an increase in tone of the uterus was recorded by palpation, and in 24 (36.36±5.9%) women, the high arousal of the uterus was confirmed by external tocography.

In the examined women, intrauterine contractions (IUC) were not detected based on palpation or external tocography regarding uterine activity. Various studies indicate that infectious factors play a significant role in the development of preterm birth (PTB), with infection of the amniotic fluid accounting for 25% to 80% of cases. Considering the importance of infectious factors in the pathogenesis of pregnancy complications, we conducted microscopic and bacteriological examinations of patients in Groups I and II.

The results of the bacterioscopic examination of endocervical secretions showed that the presence of 10 or more leukocytes in Gram-stained smears was significantly higher ($p < 0.05$) in the examined women in Groups I and II compared to the control group, with 26 (39.39 ± 6.0%) and 11 (31.42 ± 7.8%) pregnant women in Groups I and II, respectively, compared to only 2 (8.0%) in the control group.

In the main group of pregnant women, there was a significantly higher prevalence of conditional-pathogenic microflora (Enterococcus faecalis, E. coli, Staphylococcus aureus, Klebsiella) found in cervical canal samples compared to patients in the control group ($p < 0.05$). This may serve as a risk factor for preterm birth (PTB), regardless of the presence of intrauterine contractions. The study identified sexually transmitted infections (STIs) in 53 (80.30 ± 4.9%) women in Group I and 31 (88.57 ± 5.3%) in Group II during the current pregnancy.

By revealing the correlation dependence between the number of different microorganisms, we determined that in pregnant women, Lactobacillus spp. both anaerobic microorganisms and aerobic and Candida spp. there are multiple correlations between them. This shows that the quantitative ratio of bacterial species of microorganisms during non-specific vaginitis in pregnant women is even higher than Lactobacillus spp. its amount increases when stored, which leads to clinical manifestations of the infectious process in the uterus. Along with detection of information in real time, examination of excreta by PCR method and detection of conditionally pathogenic microorganisms and Lactobacillus spp. with the help of "Femoflor" system during the quantitative evaluation of the amount, it was found that anaerobic microorganisms predominated in the group of women with TOM.

The prevention of pregnancy loss caused by isthmic-cervical insufficiency can be achieved through specific treatment using both conservative and surgical methods. Surgical treatment of ICI during pregnancy is usually performed from 13 to 27 weeks (optimal period up to 20 weeks of gestation). Also, if there is a risk of ICI, it is

possible to correct the patient in the stage of preparation for pregnancy. We performed cerclage on 35 patients at risk of pregnancy loss, of whom 9 underwent laparoscopic cerclage. Transabdominal laparoscopic cerclage is performed worldwide using a standard laparoscopic technique using 4 trocars. We performed a trans-abdominal laparoscopic cerclage using a standard laparoscopic technique using 3 trocars. All over the world, patients stay in the hospital for 5-7 days after the operation. In our case, patients are discharged home after 24 hours. In our study, patients were discharged home with outpatient follow-up 24 hours after cerclage. In modern medicine, endoscopic surgical methods are rapidly advancing, providing an alternative to open surgical interventions and reducing postoperative discomfort, healing time, and length of hospital stays. When vaginal correction of isthmic-cervical insufficiency is not feasible or fails after being performed, laparoscopic abdominal cerclage is recommended for the patient.

Compared to vaginal cerclage, laparoscopic abdominal cerclage offers several advantages. During laparoscopic abdominal cerclage, the stitch is placed at the junction of the cervix, which is considered a more reliable method and aligns with modern approaches to pregnancy management and maintenance. Unlike other cerclage methods, long-term and high-dose progesterone is not used during laparoscopic abdominal cerclage.

Advantages of laparoscopic abdominal cerclage include the patient not being confined to bed rest until the end of pregnancy, reduced hospitalization, decreased incidence of preterm births, and a lower need for prolonged use of aseptic and antiseptic vaginal suppositories. Additionally, the absence or reduction of vaginal discharge complaints after laparoscopic abdominal cerclage is another advantage compared to the use of pessaries. Another benefit of laparoscopic abdominal cerclage over vaginal cerclage is that the cerclage suture remains sterile.

Due to these listed advantages, laparoscopic abdominal cerclage has a positive impact on health insurance and is

economically and socially suitable for the patient. Laparoscopic correction of ICH is performed from 10-11 weeks to 15-16 weeks of pregnancy.

During the assessment of the state of the cervix in patients with a risk of premature birth in the second trimester, it was determined that the shortening of the cervix was found in 12 (34.3±8.0%) patients, 24 -14 (40.0±8.3%) at 25 weeks, 9 (25.9±7.4%) at 26-28 weeks. TVE is performed only in risk groups (pregnancy failure, multiple pregnancy) during the first (11-14 weeks) and second screening ultrasound examination (18-21 weeks).

One of the important and unsolved problems of premature births is birth tactics. Therefore, the purpose of our study was to determine the optimal delivery tactics based on the examination during PB. It is not correct to compare prematurely born children at 22 and 28 weeks of pregnancy, therefore, all perinatal outcomes are divided into 3 groups depending on the gestation period: 22-23 weeks, 24-25 weeks, 26-28 weeks. The analysis of the causes of preterm birth (VD) and perinatal outcomes is conducted based on the duration of the current pregnancy. Preterm births are associated with the delivery of preterm infants with low birth weight.

Therefore, we began our examination of perinatal outcomes by examining the frequency of extreme low body weight (LBW) and very low body weight (VLBW). At 22-23 weeks, all children have EAB: body weight at birth varies from 400 g to 900 g, with an average weight of 720 g. At the 24-25th week of pregnancy, only 1/3 of the children have EAB, the rest have LBW: the body weight at birth varied between 740g and 1460g, and the average body weight was 1093.1g. One of the most significant problems associated with prematurity is the respiratory distress syndrome (RDS) or 'respiratory distress syndrome' in newborns. Intracerebral hemorrhage (ICH) was identified in preterm births up to the 25th week of pregnancy; it was detected in 88.2 ± 5.5% of those born between 26 and 28 weeks. This once again confirms the well-known fact: the later PB occurs in gestation, the more satisfactory the perinatal outcome. According to the data of our study, the average length of stay in the hospital for children born before 26 weeks was 88.9 days, the maximum length

of stay was 98 days. Children born at 24-25 weeks required an average of 52 days of inpatient treatment, and at 26-28 weeks - 30 days. The main cause of death of preterm infants was severe RDS and infection at 22-23 weeks and 24-25 weeks. Already at 26-28 weeks perinatal death has decreased almost 3 times. It's main causes were brain hemorrhage of 3-4 degrees and generalized infection. The main causes of perinatal death in the period of 28 weeks were IH. According to our study, a significant improvement in the perinatal outcome of VD is noted starting from 28 weeks of gestation. The data of a significant improvement in the perinatal outcome of PB after 28 weeks once again suggests that prolongation of pregnancy during PB is considered a primary task.

Based on the obtained data, a pathogenetically based algorithm for pregravid preparation, prevention and follow-up of pregnancy was developed in women who constitute the risk group for PB. The pregravid stage includes microbiological examination of the contents of the cervical canal and urine, and microscopic examination of the uterine smear. This is due to the fact that in our study, infection of the urinary system was detected in women with PB clinic. In the pregravid stage, all the patients underwent remediation of chronic infection, microscopic examination of cervical canal contents, urine and uterine smear was performed. Cervicometry every 2 weeks during the 13-28 weeks of pregnancy is important for all women in the PB risk group to monitor and predict PB. If a short cervix of less than 25 mm is detected, it is recommended to carry out the prevention of RDS of the fetus with dexamethasone in a total dose of 24 mg.

Application of new diagnostic technologies to obstetric practice, including pulse dopplerometry, color doppler mapping and 3D-reconstruction of ultrasound images in B-mode and energy doppler mode, has made it possible to study the characteristics of the couple in more detail. Successful treatment cannot be carried out without knowing the causes of PB. The implementation of active follow-up tactics of patients with TOM in the second trimester of gestation significantly improves the obstetric and perinatal prognosis, allows prolonging the pregnancy for a longer period, reduce the

frequency of premature births, perinatal losses and neonatal morbidity, and decreasing the duration of hospitalization in the second stage of babies care.

RESULTS

1. During the analysis of the gestational period, a statistically significant difference in the risk of pregnancy loss (PL) was observed starting from the 12th week of pregnancy. In the main group, PL was noted in 51.4% of cases during the 12th to 24th weeks of pregnancy, and in 49.5% of cases during the period from 22 to 28 weeks. Among patients with complicated pregnancies, a higher frequency of somatic pathology underscores the significance of this factor in the etiology of pregnancy loss. The risk of pregnancy loss during mono-infections was recorded in cases of candidiasis, ureaplasmosis, and chlamydia. Concurrent infections increase the risk of pregnancy loss across all infections. Bacteriological smears revealed a higher prevalence of Candida species, conditional pathogenic bacterial flora, and intracellular microorganisms. In the second trimester, the risk of pregnancy loss in women was associated with chronic tonsillitis (25.4±4.3%, p=0.032), chronic bronchitis (24.6±4.3%, p=0.044), chronic sinusitis (9.8±2.9%, p=0.021), and chronic pyelonephritis (9.8±2.9%, p=0.021). A significant proportion (89.5±2.9%) of the examined pregnant women with complicated gestation had somatic pathologies, including anemia (33.7±4.7%, p=0.047), autonomic vascular dystonia (31.8±4.7%, p=0.046), metabolic disorders (25.7±4.3%, p=0.032), and hypertension (17.8± 3.8%, p=0.028). Among women at risk of pregnancy loss in the second trimester, a high prevalence of gynecological diseases was observed, including nonspecific colpitis (89.2±2.9%), endocervicitis (63.5±4.7%), chronic salpingo-oophoritis (60.5±4.7%), and chronic endometritis (34.1±4.6%) [2, 4, 5].

2. Risk factors for pregnancy loss include conception after in vitro fertilization (24.88±4.3%, $p<0.05$); spontaneous abortions (54.14±4.9%, $p<0.05$); history of preterm births (36.83±4.3%, $p<0.05$); prolonged risk of pregnancy loss in the first trimester (63.41±4.7%, $p<0.05$); changes in the vaginal biosenosis characterized by conditional pathogenic microflora (69.88±4.8%, $p<0.05$); and sexually transmitted infections (33.75±4.3%, $p<0.05$) [6, 9].
3. Based on the obtained data, a pathogenetically justified algorithm for pregravid preparation, pregnancy prophylaxis, and monitoring has been developed for women in the risk group for hypertension during the second trimester of gestation. Laparoscopic correction of cervical insufficiency is performed between the 10th and 11th weeks to the 15th and 16th weeks of pregnancy. Transabdominal laparoscopic cerclage was carried out using a standard laparoscopic technique with three trocars. During abdominal laparoscopic cerclage, the stitch is placed at the cervical junction, which is considered a more reliable method and aligns with modern approaches to pregnancy monitoring and maintenance. Unlike other cerclage methods, long-term and high-dose progesterone is not used during laparoscopic abdominal cerclage. Advantages of abdominal laparoscopic cerclage include the patient's freedom from bed rest until the end of pregnancy, reduced need for hospitalization, decreased incidence of preterm births, and a lower necessity for prolonged use of aseptic and antiseptic vaginal suppositories [1, 8].
4. In the absence of other pathologies, the delivery tactics during preterm births are determined based on the duration of gestation: Births up to 28 weeks are more optimal to be carried out by natural childbirth methods - because there are no differences in the perinatal outcome depending on the delivery tactics during these periods of gestation. In the case of a gestational period of 28-30 weeks, the optimal delivery tactic is considered to be a cesarean section with the

extraction of the fetus in the intact fetal membrane. This approach allows for improved perinatal outcomes compared to natural deliveries, primarily due to the reduction in the frequency of intracranial hemorrhages in preterm infants. From the total number of PB to the 26th week of gestation, 4.95% PB occurred. The frequency of extreme early PB (26-28 weeks) was 54.55% of cases, early PB (29-32 weeks) was 19.8% of cases, PB occurring in the period of 33-36 weeks of pregnancy was 20.70% of cases. Among the examined patients, the frequency of operative births was 73.27%. Only 4.95% of newborns were healthy, extreme low body weight was recorded in 5.94% of cases. Very low birth weight was observed in 14.85% of children born in the period of 27-36 weeks. Perinatal mortality was 7.92% (8 cases). The highest frequency of perinatal losses occurred at the 28th week of gestation [2, 3, 7].

5. Active monitoring of the pregnant woman significantly improves perinatal prognosis, allowing the pregnancy to be carried to a more favorable duration of gestation. During pregnancy, the immune system plays an important role both in maintaining the normal course of pregnancy and in the development of complications. SNA - a, IL-2, IL-6, IL-4 and IL-10 are considered to be the main cytokines involved in the development of complications. The analysis of the dynamics of cytokines by trimesters in the main group of pregnant women showed that the change in their amount had the following tendency: their amount increased in the first trimester, decreased in the second trimester (after treatment) and increased again in the cervical mucus in the third trimester of pregnancy [10].

PRACTICAL RECOMMENDATIONS

1. Pregnant women with TOM in the II trimester of gestation should be considered as patients with developing double

incompatibility and in such patients, the treatment of double incompatibility should be started as soon as possible.

2. In the second trimester of pregnancy, women with three or more intranatal losses or the risk of early delivery (without a specific cause identified other than ICI) should be offered cervical cerclage after screening for chromosomal pathologies during the 12-14 week period.
3. Laparoscopic cerclage should be considered in women with a history of premature birth and failure of vaginal cervical cerclage in previous pregnancies.
4. In order to improve the accuracy of the diagnosis and the prognosis of the course of the disease, it is recommended to thoroughly study the composition of the cytokines TNF-α, IL-2, IL-4, IL-6 and IL-10 in the cervical mucus during the examination of patients with ICI.

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ABBREVIATIONS

STI - Sexually transmitted infections
VLBW - Very low birth weight
ELBW - Extremely low birth weight
RPL - Risk of pregnancy loss
TPPL - Threat of preterm pregnancy loss
PPL - Preterm pregnancy loss
IL - Interleukin
ELISA - Enzyme-linked immunosorbent assay
II - Isthmicocervical insufficiency
IH - Intraventricular hemorrhage
PI - Pulsatility index
PCR - Polymerase chain reaction
RDS - Respiratory distress syndrome
RI- Resistance index
SDR - Systolic-diastolic ratio
TNF - Tumor necrosis factor
TLR - Toll-like receptors
TVS - Transvaginal sonography
RDS - Respiratory distress syndrome
CP - Cerebral palsy
CL - Cervical length
USE - Ultrasound examination
PB - Preterm births

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