

DIAGNOSIS AND MANAGEMENT TACTICS OF PATIENTS WITH ISTHMIKO-CERVICAL INSUFFICIENCY

Djakhanov Obidjon Olimovich

Email: djaxanov.obidjon@bsmi.uz <https://orcid.org/0009-0006-4011-5277>

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

Resume: The article is devoted to diagnostic methods, therapeutic options, and management algorithms for patients with isthmio-cervical insufficiency (ICI). Acquired and congenital abnormalities of the cervix are risk factors for the development of ICI. The diagnosis is valid only during pregnancy. A shortening of the length of the cervix of less than 25 mm indicates the presence of ICI and the risk of premature birth. The optimal time for the initial assessment of the length of the cervix is 16-20 weeks. If the length of the cervix is more than 25 mm, but less than 30 mm, micronized progesterone 200 mg is prescribed into the vagina for preventive purposes from 19 to 34 weeks. When ICI is detected after 24 weeks, the method of choice is the appointment of micronized progesterone and the installation of an obstetric discharge pessary. Shortening of the length of the cervix up to 24 weeks of pregnancy is an indication for surgical correction and cerclage followed by micronized progesterone therapy. The use of a differentiated management algorithm for patients with ICI reduces the likelihood of unexpected premature birth and neonatal morbidity and mortality. **Keywords:** isthmio-cervical insufficiency, premature birth, miscarriage, cerclage, obstetric pessary, micronized progesterone, cervicometry, elastometry.

Key words: isthmio-cervical insufficiency (ICI), pregnancy, premature birth, cervix, manifest, length of cervix (L of C).

Резюме: Статья посвящена методам диагностики, возможностям терапии и алгоритмам ведения пациенток с истмико-цервикальной недостаточностью (ИЦН). Факторами риска развития ИЦН являются приобретенные и врожденные аномалии шейки матки. Диагноз правомочен только во время беременности. Укорочение длины шейки матки менее 25 мм свидетельствует о наличии ИЦН и риске преждевременных родов. Оптимальными сроками для первичной оценки длины шейки матки являются 16–20 нед. При длине шейки матки более 25 мм, но менее 30 мм с профилактической целью с 19 до 34 нед назначается микронизированный прогестерон по 200 мг во влагалище. При выявлении ИЦН в сроки после 24 нед методом выбора являются назначение микронизированного прогестерона и установка разгрузочного акушерского pessaria. Укорочение длины шейки матки в сроки до 24 нед беременности является показанием для хирургической коррекции и серкляжа с последующей терапией микронизированным прогестероном. Применение дифференцированного алгоритма ведения пациенток с ИЦН снижает вероятность неожиданных преждевременных родов и неонатальной заболеваемости и смертности. **Ключевые слова:** истмико-цервикальная недостаточность, преждевременные роды, невынашивание беременности, серкляж, акушерский pessарий, микронизированный прогестерон, цервикометрия, эластометрия.

Rezyume: Maqola diagnostika usullari, terapiya imkoniyatlari va ishemik-servikal yetishmovchiligi (ISY) bo'lgan bemorlarni boshqarish algoritmlariga bag'ishlangan. ISY rivojlanishining xavf omillari serviksin orttirilgan va tug'ma anomaliyalaridir. Tashxis faqat homiladorlik paytida vakolatli. Bachadon bo'yni uzunligining 25 mm dan kam qisqarishi ISY mavjudligini va erta tug'ilish xavfini ko'rsatadi. Bachadon bo'yni uzunligini dastlabki baholash uchun maqbul vaqt 16-20 hafta. Bachadon bo'yni uzunligi 25 mm dan ortiq, ammo 30 mm dan kam bo'lsa, profilaktika maqsadida 19 dan 34 haftagacha vaginada 200 mg mikronizatsiyalangan progesteron buyuriladi. Agar ISY 24 haftadan keyin aniqlansa, mikronizatsiyalangan progesteronni tayinlash va tushirish akusherlik pessarini o'rnatish tanlov usuli hisoblanadi. Homiladorlikning 24 xaftaligiga qadar bachadon bo'yni uzunligining qisqarishi jarrohlik tuzatish va serklaj uchun ko'rsatma bo'lib, undan keyin mikronizatsiyalangan progesteron terapiyasi qo'llaniladi. ISY bilan og'rigan bemorlarni boshqarishning tabaqalashtirilgan algoritmini qo'llash kutilmagan erta tug'ilish va neonatal kasallanish va o'lim ehtimolini kamaytiradi. Kalit so'zlar: istmiko-servikal etishmovchilik, erta tug'ilish, homiladorlikning yo'qolishi, serklaj, akusherlik pessari, mikronizatsiyalangan progesteron, servikometriya, elastometriya

Relevance : Premature birth is an important medical and social problem, the solution of which will not only improve the health of the population, but also reduce the incidence of early neonatal mortality and disability. The causes of miscarriage include endocrine (20%), autoimmune (20%), anatomical (16%), infectious (9%) and translocation (3%). However, about 43% of cases of premature birth occur for unknown reasons, being included in the group of idiopathic [1]. Among the potentially preventable factors, isthmio-cervical insufficiency (ICI) stands alone. The term ICI implies a violation of the blocking ability of the cervix, manifested by its painless shortening and opening, followed by early termination of pregnancy [2]. The frequency of ICI ranges from 0.2 to 2%, however, in the group of patients with premature birth at 22-32 weeks, it reaches 40% [3]. The development of ICI is based on acquired (ruptures, conization, infectious lesions) or congenital changes of the cervix: malformations, connective tissue dysplasia, undifferentiated and syndromic (Ehlers–Danlos syndrome) [4, 5]. A history of indications of surgical treatment cervical malformations, detected malformations, or early termination of previous pregnancies only indicate the risk of miscarriage due to possible heart failure, but are not grounds for making a diagnosis [6, 7]. The diagnosis of ICI is valid only during pregnancy; outside of pregnancy, it cannot be confirmed or refuted. Previously proposed methods for assessing the closure function of the cervix (Gegar dilators, hysteroscopy) are not reliable, but in some cases they can identify malformations and other diseases of the uterus (Table. 1) [8]. Clinically, the formation of ICI may be accompanied by a feeling of heaviness in the pelvis and pain in the lumbar region. In addition, it is possible to change the amount and color of vaginal discharge from transparent, white or light yellow to pink, dark or powdery. ICI most often manifests itself between the 14th and 20th weeks of pregnancy [3, 9-11].

Diagnosics:

Diagnosis of ICI The diagnosis of ICI is based on the totality of the results of clinical examination and transvaginal ultrasound examination (ultrasound).

Ultrasound cervicometry is most informative at 16-24 weeks and only with the help of transvaginal examination. The length of the closed part of the cervical canal during these

periods should exceed 30 mm. Before 16 and after 30-32 weeks, the significance of the method is limited and the clinical assessment of the state of the birth canal comes to the fore [3, 10]. Shortening of the length of the cervix (LofC) < 25 mm in terms of up to 24 weeks indicates a significant risk of miscarriage. Leading international organizations on prenatal medicine (the Foundation for Fetal Medicine and the International Society for Ultrasound in Obstetrics and Gynecology) recommend evaluating LofC starting at 14 weeks [11]. At the same time, the following rules must be observed [2, 11-14]:

- Ultrasound is performed only by transvaginal access;
- the bladder should be emptied;
- the sensor should not apply pressure on the cervix;
- the cervix should occupy up to 75% of the image area;
- the lower pole of the bladder of a pregnant woman should be visualized;
- the thickness of the anterior and posterior lips of the cervix should be approximately the same;
- the cervical canal should look slightly concave due to the sensor located in the anterior arch of the vagina. With the rectilinear shape of the cervical canal, its length is measured as the size from the outer to the inner pharynx. However, most often the cervical canal has a curved shape, and if the canal line deviates from the straight line by more than 5 mm, the measurement consists of the sum of 2 straight segments (Fig. 1) [2]. In multiple pregnancies, breast cancer is not a criterion for assessing the risk of miscarriage, since the pathogenesis of premature birth in multiple pregnancies in most cases is not associated with heart failure [15, 16]. When making a diagnosis of ICI, not only the length of the closed part of the cervical canal is important, but also the consistency of the cervix.

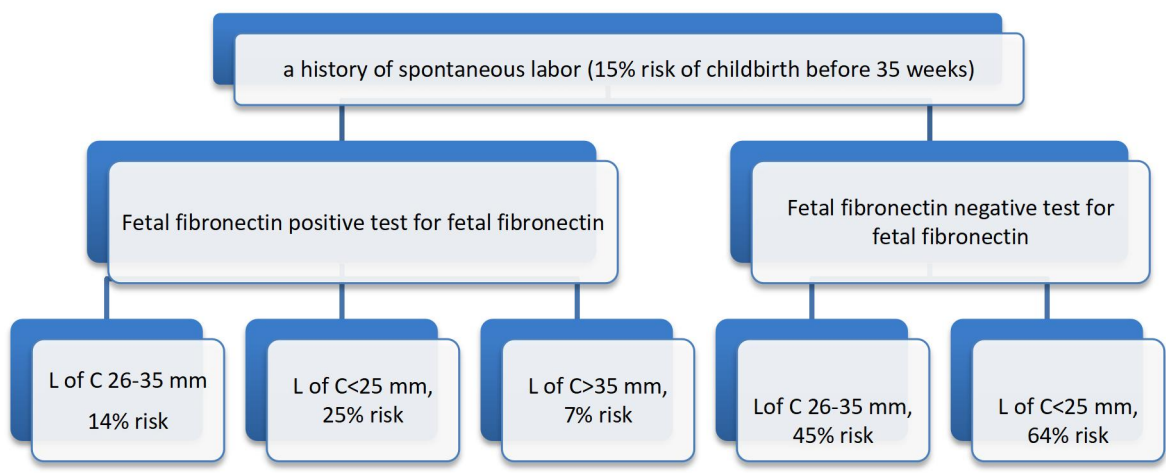
It is possible to assess the density of cervical tissues during obstetric examination using the Bishop scale, as well as using ultrasound elastography, which has been used for this purpose since 2017 [17]. Elastography is an ultrasound scanning technology that makes it possible to evaluate tissue elasticity (stiffness) in real time. The essence of the method lies in the ability of biological tissues to deform when an external force is applied. The degree of deformability of tissues directly depends on their histological structure. The softer the fabric, the easier it changes its shape. The ultrasound signal returns from softer tissues faster than from hard ones after deformation, which is reflected in the scale of the color shades. A special color scale of elasticity (stiffness) has been developed for ultrasound diagnostic devices, according to which the degree of deformation corresponds to a certain color: easily displaced soft tissues are encoded in red, tissues with medium displacement are green, and hard-to-displace dense tissues are blue (Fig. 2) [18, 19].

In addition to the qualitative color evaluation of the results obtained, digital parameters are used. The strain coefficient is the difference in the displacement obtained in the study area to the control area. Elastography provides information about the internal stiffness of the selected area of the cervix. This is a parameter that cannot be estimated by manual

examination. To date, ultrasound elastography seems to be a very promising method of assessing the cervix at all stages of pregnancy. The data obtained using elastography make it possible to predict the probability of premature birth and termination of pregnancy up to 22 weeks [19-21]

Among the many laboratory tests, the prognostic significance of which has been proven, the test for the determination of fetal fibronectin has become the most widespread. The combined use of this test and cervicometry increases their sensitivity and specificity (Fig. 3). Receiving two consecutive negative test results indicates an extremely low probability (~1%) of premature birth within the next 2 weeks [22, 23]. The combined use of cervicometry and the fetal fibronectin test makes it possible to more accurately predict the risk of premature birth. If the length of the closed part of the cervical canal was more than 15 mm at 23 weeks of pregnancy, the risk of premature birth before 32 weeks does not exceed 4%. However, with the development of clinical manifestations of threatening premature birth and a cervical canal length of less than 15 mm, the probability that labor will occur in the next 7 days reaches 49%. And in the case of DSM>15 mm, the risk of up to 1% is used! At the same time, the determination of a positive test for fetal fibronectin in the cervical mucus indicates that labor will occur in 7-10 days [24].

A combined approach to predicting the risk of premature birth



Treatment of pregnant women with ICI.

The management tactics of patients with ICI is primarily determined by the gestation period and medical history. In the case of an already diagnosed ICI, depending on the duration of pregnancy, the issue of either surgical correction or the use of an obstetric unloading pessary is being resolved. All patients, regardless of the chosen tactics, are prescribed micronized progesterone therapy intravaginally for up to 34 weeks [16, 22]. In the presence of a history of premature birth and/or pregnancy losses in the second trimester, ultrasound and

cervicometry begin at 12-14 weeks in order to diagnose ICI in a timely manner. If a shortening of the length of the closed part of the cervical canal is less than 25 mm, surgical correction (cerclage) is the method of choice; Table. 2. With a Lof C of more than 25 mm, micronized progesterone 200 mg is prescribed in the vagina for preventive purposes from 19 to 34 weeks. Administration of vaginal progesterone to women with a shortened cervix reduces the likelihood of unexpected premature birth and neonatal morbidity and mortality, and is also cost-effective [25, 26]. Patients without a burdened medical history, according to the order of the Ministry of Health of the Russian Federation dated 12.11.2012 No. 572n "On approval of the Procedure for providing medical care in the field of obstetrics and gynecology (with the exception of the use of assisted reproductive technologies)", the ultrasound assessment of L of C is performed during the screening morphological examination of the fetus (18-24 weeks) [2]. If a shortening of the cervix to 26-30 mm is detected, weekly cervicometry and a fetal fibronectin test are indicated. With a shortening of the cervix of less than 25 mm in the period up to 24 weeks of pregnancy, it is advisable to perform surgical correction of ICI followed by therapy with micronized progesterone 200 mg intravaginally for up to 34 weeks. After 24 weeks of pregnancy, the cervix is not sutured and the method of choice is the use of micronized progesterone and the use of an obstetric pessary (Fig. 4) [10, 22, 24]. Taking into account the various factors leading to the formation of ICI, a differentiated approach to the choice of patient management tactics was developed (Fig. 5) [3, 11, 24].

For patients with impaired blocking function of the cervix, which was formed due to previous injuries (conization, rupture of the cervix in childbirth, multiple intrauterine interventions, congenital disability), surgical correction using micronized progesterone is the method of choice. According to the results of a systematic review, which included an independent study, 2 prospective and 7 retrospective cohort studies, it was proved that applying cerclage to patients with ICI and visible membranes increases the likelihood of a favorable pregnancy outcome (neonatal survival with cerclage is 71% versus 43% using only wait-and-see tactics) [27]. Suturing of the cervix is not performed in the presence of signs of intrauterine infection, bleeding, and the absence of conditions [25]. In case of detection of an abnormal angle between the internal pharynx of the cervix and the uterine wall, it is advisable to use an obstetric discharge pessary. Pessaries are designed to change the axis of the cervical canal and shift the weight of the contents of the uterus from the cervix. By changing the angle of the cervix, the pessary also prevents the opening of the internal pharynx and thus provides protection against infection [24].

Nonsteroidal anti-inflammatory drugs. In the course of 3 independent studies, it was found that the use of indomethacin for cervical shortening at 14-27 weeks does not reduce the likelihood of premature birth to 35 weeks, but reduces the likelihood of childbirth to 24 weeks [26]. Most often, therapy with nonsteroidal anti-inflammatory drugs is performed before surgical correction of ICN. Indomethacin is prescribed 50 mg orally every 6 hours for 48 hours. The drug can be used for up to 32 weeks, after which its use increases the risk of premature closure of the arterial duct in the fetus and is impractical.

Lifestyle. Lifestyle changes in patients with ICN did not show the desired result, but it is recommended to adhere to bed rest, limit physical exercise and refrain from sexual intercourse. Smoking has been proven to be an independent risk factor for the development of premature birth, but it is not associated with the formation of ICN [3].

The conclusion of the ICI is an independent and significant risk factor for miscarriage. Timely diagnosis in most cases allows either to completely prevent premature birth, or to prolong pregnancy until the fetus reaches the period of viability. The provision of high-quality medical care to patients at risk of premature birth is based on a thorough history collection with an assessment of all significant factors, exclusion or confirmation of connective tissue dysplasia, early cervicometry and elastometry to assess the closing function of the cervix. It is advisable for pregnant women from the high-risk group to consider either preventive circulation followed by micronized progesterone therapy, or the use of progesterone monotherapy under the control of cervicometry. Surgical correction of ICI is optimal for up to 24 weeks, and before it is performed, the use of indomethacin for 48 hours is effective. In the case of late diagnosis of ICI, the method of choice is a combination of an obstetric discharge pessary and intravaginal administration of micronized progesterone. The terms of use of micronized progesterone have been revised, and currently the duration of use of the drug ranges from 19 to 34 weeks. The unloading obstetric pessary, as well as the sutures from the cervix, must be removed at 37 weeks of pregnancy.

Bibliography:

1. McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. *Fertil Steril* 2014; 101 (4): 1026–30.
2. Буланов М.Н. Ультразвуковая диагностика заболеваний шейки матки. М.: Видар-М, 2017. / Bulanov M.N. Ultrazvukovaia diagnostika zabolevanii sheiki matki. M.: Vidar-M, 2017. [in Russian]
3. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No.142: Cerclage for the management of cervical insufficiency. *Obstet Gynecol* 2014; 123: 372.
4. Rackow BW, Arici A. Reproductive performance of women with mllerian anomalies. *Curr Opin Obstet Gynecol* 2007; 19: 229.
5. Shah PS, Zao J; Knowledge Synthesis Group of Determinants of preterm/LBW births. Induced termination of pregnancy and low birth weight and preterm birth: a systematic review and meta-analyses. *BJOG* 2009; 116: 1425.
6. Vyas NA, Vink JS, Ghidini A et al. Risk factors for cervical insufficiency after term delivery. *Am J Obstet Gynecol* 2006; 195: 787.
7. Warren JE, Silver RM, Dalton J et al. Collagen 1Alpha1 and transforming growth factor-beta polymorphisms in women with cervical insufficiency. *Obstet Gynecol* 2007; 110: 619.
8. Сидельникова В.М. Привычная потеря беременности. М.: ТриадаХ, 2000. / Sidelnikova V.M. Privychnaia poteria beremennosti. M.: Triada-Kh, 2000. [in Russian]
9. Chan YY, Jayaprakasan K, Tan A et al. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. *Ultrasound Obstet Gynecol* 2011; 38: 371.

10. Romero R, Lockwood CJ. Pathogenesis of spontaneous preterm labor. In: Creasy RK, Resnik R, Iams JD et al. (Eds). *Creasy&Resnik's Maternal Fetal Medicine*. Saunders, 2009.

11. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol* 2012; 206: 376.

12. Berghella V, Rafael TJ, Szychowski JM et al. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet Gynecol* 2011; 117: 663.

13. Berghella V, Mackeen AD. Cervical length screening with ultrasound-indicated cerclage compared with history-indicated cerclage for prevention of preterm birth: a meta-analysis. *Obstet Gynecol* 2011; 118: 148.

14. Iams JD, Cebrik D, Lynch C et al. The rate of cervical change and the phenotype of spontaneous preterm birth. *Am J Obstet Gynecol* 2011; 205: 130. 15. Berghella V, Figueroa D, Szychowski JM et al. 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length. *Am J Obstet Gynecol* 2010; 202: 351.e1.

16. Rafael TJ, Mackeen AD, Berghella V. The effect of 17 a -hydroxyprogesterone caproate on preterm birth in women with an ultrasound-indicated cerclage. *Am J Perinatol* 2011; 28: 389.

17. Myers KM, Feltovich H, Mazza E et al. The mechanical role of the cervix in pregnancy. *J Biomech* 2015; 48 (9): 1511–23.

18. Shiina T, Nightingale KR, Palmeri ML et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; 41 (5): 1126–47. 19. Thomas A, Degenhardt F, Farrokh A et al. Significant differentiation of focal breast lesions: calculation of strain ratio in breast sonoelastography. *Acad Radiol* 2010; 17 (5): 558–63.

20. Molina FS, Gómez LF, Florido J et al. Quantification of cervical elastography: a reproducibility study. *Ultrasound Obstet Gynecol* 2012; 39 (6): 685–9. 21. Fruscalzo A, Londero AP, Schmitz R. Quantitative cervical elastography during pregnancy: influence of setting features on strain calculation. *J Med Ultrason* 2015; 42 (3): 387–94.

22. Conde-Agudelo A, Romero R, Nicolaidis K et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. *Am J Obstet Gynecol* 2013; 208: 42.e1.

23. Ehsanipoor RM, Seligman NS, Saccone G et al. Physical Examination Indicated Cerclage: A Systematic Review and Meta-analysis. *Obstet Gynecol* 2015; 126: 125.

24. Alfirovic Z, Owen J, Carreras Moratonas E et al. Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. *Ultrasound Obstet Gynecol* 2013; 41: 146.
25. Gorski LA, Huang WH, Iriye BK, Hancock J. Clinical implication of intraamniotic sludge on ultrasound in patients with cervical cerclage. *Ultrasound Obstet Gynecol* 2010; 36: 482.
26. Vousden N, Hezelgrave N, Carter J et al. Prior ultrasound-indicated cerclage: how should we manage the next pregnancy? *Eur J Obstet Gynecol Reprod Biol* 2015; 188: 129.
27. Goya M, Pratcorona L, Merced C et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012; 379: 1800.
28. Roberge S, Nicolaidis KH, Demers S et al. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; 41: 491–9.