

Comparative Evaluation of the Effectiveness of the Combined Method of Correction of Isthmic-cervical Insufficiency Using Dr. Arabin's Perforated Silicone Obstetric Pessary with the Addition of Vaginal and Sublingual Tableted Micronized Progesterone

O. M. Nosenko ^{1*}, F. O. Khancha ², G. V. Rutynska ³

^{1*} Professor Doctor of Medicine, Professor of the Department of Obstetrics and Gynecology of ONMedU, Odesa, Ukraine

² Ph.D., Assistant of the Department of Obstetrics and Gynecology of the Donetsk National Medical University, Kropivnytskyi, Ukraine

³ Ph.D., Doctor-sonologist, LLC "Profile hospital AIRMED", Odesa, Ukraine

ARTICLE INFO

2024 Volume 1

<https://www.doi.org/ccrcr.2024.tgc.0289>

Article History:

Received: Apr 05, 2024

Accepted: Apr 14, 2024

Published: May 01, 2024

Citation: O.M. Nosenko, F. O. Khancha, G. V. Rutynska. (2024). Comparative evaluation of the effectiveness of the combined method of correction of isthmic-cervical insufficiency using Dr. Arabin's perforated silicone obstetric pessary with the addition of vaginal and sublingual tableted micronized progesterone. *Chronicles of Clinical Reviews and Case Reports*, The Geek Chronicles, 1, 1-19.

Copyright: © 2024 O.M. Nosenko, this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Keywords: cervical insufficiency, combined technique of correction, obstetric perforated pessary Dr. Arabin, vaginal tablets of micronized progesterone, sublingual tablets of micronized progesterone, results of pregnancy and childbirth.

ABSTRACT

Aim: Data on the effectiveness of the combined method of correction of cervical insufficiency (CI) with the application of a pessary and the intake of micronized progesterone are innumerable and superbly. Individual studies are devoted to the study of the use of sublingual form of micronized progesterone in CN. The purpose of the study was a comparative assessment of the effectiveness of a combined therapeutic and prophylactic method for correcting CI by using Dr. Arabin's vaginal perforated obstetric pessary and various forms of tableted micronized progesterone - vaginal and sublingual.

Material and methods: 215 pregnant women with CI were under observation. The main group included 129 pregnant women with CI, in whom therapeutic and preventive measures included a combination of applying an obstetric perforated pessary by Dr. Arabin and taking a sublingual form of micronized progesterone 100 mg three times a day up to 36 weeks of pregnancy. The replenishment included 86 pregnant women treated with CI with Dr. Arabin's vaginal perforated obstetric pessary and micronized progesterone vaginal tablets 200 mg twice daily up to 36 weeks' gestation. All women during the gestational period also received vitamin-mineral complexes for pregnant women, ω 3-polyunsaturated fatty acids and magnesium preparations. It was assessed course of pregnancy, obstetric and perinatal consequences.

Results: The study of further combined methods in the correction of CI led to similar results in vagity and fluctuations: there was no statistically significant difference between the main group and the group in the frequency of early opening of the fruit membranes ($\chi^2 = 6.65\%$ vs. 0.47), flat up to 32 strokes (1.55% versus 4.65%, $\chi^2=1.83$, $p=0.18$) and flat in 33-36 strokes (4.65% versus 6.98%, $\chi^2=0.53$, $p=0.47$), term slopes (93.80% versus 88.37%, $\chi^2=1.98$, $p=0.16$), operative delivery by cesarean section (13.95% vs. 2.33% versus 6.98%, $\chi^2=2.78$, $p=0.10$), neonatal illness (4.65% versus 10.47%, $\chi^2=2.69$, $p=0.10$), people babies with less than 1,500 g (1.55% vs. 5.81%, $\chi^2=2.98$, $p=0.08$), middle-weight babies (3,420.24±48.98 vs. 3,360.23± 66.38 g, $p=0.47$). With equal compliance of cuval-prophylactic visits, it was established that the breeds were evaluated in the obstetric pessary + sublingual progesterone group at 9.19 ± 0.11 points, in the obstetric pessary + vaginal progesterone group - at 7.83 ± 0.01 points.

Conclusion. Combined methods of CI correction using Dr. Arabin's vaginal perforated obstetric pessary in combination with tablet micronized progesterone are effective and safe when using both vaginal and sublingual forms of progesterone, but the method of using a pessary and sublingual progesterone is more optimal, convenient and compliant. Both techniques can be widely used in clinical practice.

Introduction

The competent human cervix is a complex organ that undergoes extensive changes throughout pregnancy and childbirth. The complex process of cervical remodelling that occurs during pregnancy involves timely biochemical cascades, interactions between extracellular and cellular compartments, and cervical stromal infiltration by inflammatory cells. Any disturbance in this temporal interaction can lead to premature ripening of the cervix, inhibition of its function as a sphincter, insufficiency of the obturation function of the cervix, and premature birth or miscarriage [49, 84].

Cervical insufficiency (CI) implies a violation of the closing ability of the cervix, manifested by its painless shortening and opening without increased contractility of the uterus, followed by early termination of pregnancy [3, 5, 17]. CI is rarely a clear and well-defined clinical entity, being only part of a larger and more complex syndrome of spontaneous preterm birth [47, 84].

Epidemiological studies suggest an approximate incidence of CI of 0.5% in the general obstetric population and 8% in women with a history of previous midtrimester miscarriage [80]. CI is the cause of 15-40% of late miscarriages and up to 30% of premature births. After termination of pregnancy in the II trimester, the risk of losing the next pregnancy increases tenfold [2].

A well-known sign of cervical insufficiency is the appearance of habitual episodes of miscarriage during the second trimester of pregnancy, which is clinically manifested by painless dilation of the cervix with subsequent protrusion, rupture of the amniotic membranes, and expulsion of a usually live foetus, with little uterine activity [403]. Therefore, the diagnosis of CI is traditionally given to patients with a history of repeated late miscarriages and/or early preterm births, in which the main mechanism is the "inability of the cervix to remain closed" [2, 80]. Most often, CI manifests between the 14th and 20th weeks of pregnancy [32, 68].

Both abroad and in our country, numerous methods of operative and non-operative treatment of CI have been proposed both during and outside pregnancy [27, 29, 42, 58, 81]. All of them have a common goal - to prevent the opening of the cervix as a factor in premature birth. Numerous methods and modifications of surgical treatment of CI have been used for several decades. This is due to the fact that none of the existing treatment methods has 100% efficiency [88]. The main modern tactics of CI management are vaginal progesterone, cerclage, pessary and the use of omega-3 polyunsaturated fatty acids [15, 39, 50, 85, 89].

Progesterone reduces uterine smooth muscle contraction and reduces the inflammatory process involved in labour. Progesterone is considered a key hormone in maintaining pregnancy, and if the decline in progesterone activity occurs in the middle trimester, the cervix may shorten, leading to preterm birth. Progesterone blockade can lead to clinical, biochemical, and morphological changes associated with cervical ripening [36]. Progesterone has been shown to be effective in reducing rates of preterm birth and neonatal mortality compared to placebo [48].

S.S. Hassan et al. (2011) [44] conducted a multicentre, randomized, double-blind, placebo-controlled trial in asymptomatic women with a singleton pregnancy and ultrasonographically short cervix (10–20 mm) at 19 + 0–23 + 6 weeks of gestation. 458 (vaginal progesterone gel, n = 235; placebo, n = 223) were included in the analysis. Women treated with vaginal progesterone had a lower rate of preterm birth by 33 weeks than those treated with placebo (8.9% (n = 21) vs. 16.1% (n = 36); relative risk (RR) 0, 55 [0.33-0.92]; P = 0.02). The effect remained significant after adjustment for covariates (adjusted RR, 0.52 [0.31-0.91]; P = 0.02). Vaginal progesterone was also associated with a significant reduction in preterm birth at 28 weeks (5.1% vs. 10.3%; RR 0.50 [0.25-0.97]; P = 0.04) and 35 weeks (14.5%

vs. 23.3%; RR 0.62 [0.42-0.92]; P = 0.02), respiratory distress syndrome (3.0% vs. 7.6 %; RR 0.39 [0.17-0.92]; P = 0.03), any neonatal morbidity or mortality (7.7% vs. 13.5%; RR 0.57 [0.33-0.99]; P = 0.04) and birth weight < 1500 g (6.4% (15/234) vs. 13.6% (30/220); RR 0.47 [0.26-0.85]; P = 0.01). There were no differences in the incidence of treatment-related adverse events between groups. The authors concluded that mid-trimester use of vaginal progesterone gel in women with sonographically short cervix is associated with a 45% reduction in preterm birth by 33 weeks' gestation and improved neonatal outcome.

Meta-analysis by R. Romero et al. (2012) [71] of individual patient data showed that in asymptomatic women with single or multiple pregnancies and a short cervix, the use of progesterone leads to lower rates of preterm birth (26% vs. 36%; odds ratio (OR) 0.45 [0.25-0.80]) and lower rates of perinatal mortality, although this difference did not reach statistical significance (15% vs. 17%; OR 0.69 [0.38-1.30]).

A recent systematic review and meta-analysis of individual patient data from randomized trials that included data from the OPPTIMUM trial showed that vaginal progesterone supplementation significantly reduced the risk of preterm birth and neonatal morbidity/mortality in singleton pregnancies with a cervical length ≤ 25 mm [34]. In view of these findings, the American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have published recommendations that patients should receive progesterone therapy [76, 82].

At the same time, a subgroup analysis of women with a history of spontaneous preterm birth showed that vaginal progesterone had no effect on either obstetric or perinatal outcomes, but showed a possible effect of treatment on the combined neonatal outcome (OR 0.48 [0.29-0.79]) [59]. The reason why progesterone is not effective in all treated patients remains unclear [87]. One reason may be that we don't fully understand how progesterone works, especially

in the cervix. There is evidence that progesterone can regulate the remodelling of the cervix by various methods [45, 54]. It can change the function of cells, which, in turn, can modulate the components of the cervical extracellular matrix, that is, the synthesis of collagen [31], glycosaminoglycans [55], which, in turn, can affect the organization of the extracellular matrix.

Of course, withdrawal of progesterone is important for the ripening phase of the cervix, which occurs immediately before childbirth. In mice with an abnormally high level of progesterone at the end of pregnancy (due to a violation of progesterone metabolism), there is a violation of cervical ripening [67]. In addition, the progesterone antagonist mifepristone induces cervical ripening in women [61, 86]. Finally, cervical remodelling is thought to be associated with an inflammatory process, and progesterone has an anti-inflammatory effect that may moderate the remodelling process. However, data on how progesterone may counteract inflammation are mixed [41].

Reports of some randomized trials show that adjunctive therapy using omega-3 long-chain polyunsaturated fatty acids significantly reduces the incidence of "recurrent preterm birth" [39, 63]. Evidence from documented human and animal reports has shown that the ω -3 and ω -6 series of essential fatty acids, including their respective "eicosanoid metabolites", strongly influence the duration of pregnancy and parturition [21, 39]. Prostaglandins of the second class are involved in the remodelling of the connective tissue, which is associated with the ripening of the cervix and rupture of the membranes. In the absence of sexually transmitted infections, premature birth is characterized by a lower expression of prostaglandins in the tissues of the reproductive tract, which leads to a decrease in the expression of induced cyclooxygenase. Pregnant women who have delivered preterm often have high blood levels of ω -6 fatty acids but low levels of ω -3 fatty acids, despite a reduced rate of prostaglandin production [21, 39]. A number of studies in the maintenance of pregnancy with ω -

3 fatty acid supplements revealed a significant decrease in the frequency of premature birth, however, an increase in the weight of the new born is possible [39, 72, 73].

The method of surgical correction of CI has more than half a century of history with ambiguous results, its supporters and opponents. According to the recommendations of the American Society of Obstetricians and Gynaecologists in 2014, surgical correction is recognized as the therapy of choice in women with a history of premature birth and a dynamic change in the length of the cervix, opening of the internal os according to transvaginal ultrasound [14, 26].

Cervical cerclage is a surgical procedure first introduced by V. N. Shirodkar (1955) [75] and I. A. McDonald (1957) [56] in the mid-1950s and is now used prophylactically for women with recurrent second-trimester loss, suggesting CI. A cerclage based on anamnesis is usually applied between the 12th and 15th weeks of pregnancy, based on an extremely difficult obstetric history, for example, multiple losses in the second trimester due to painless cervical dilatation. Ultrasound-guided cerclage is defined as a cerclage applied usually between the 16th and 23rd weeks of pregnancy, after transvaginal ultrasound has determined a cervical length of < 20 mm in a woman without cervical dilatation. A cerclage demonstrated by physical examination is defined as a cerclage applied usually between 16 and 23 weeks of gestation due to cervical dilation of one or more centimetres detected by physical (manual) examination [39]. Cervical cerclage consists of a seam around the cervix, acts as a physical as well as a biochemical barrier, protecting the amniotic membrane from ascending pathogens [43, 79]. The effectiveness and safety of this procedure remains controversial [20].

According to the most recent 2017 Cochrane review [20] of the effectiveness of cervical cerclage in singleton pregnancy, which included 15 RCTs (3,490 women), overall, cerclage likely results in a reduced risk of perinatal death compared with no cerclage, although CI crosses the line of no effect (OR 0.82 [0.65-1.04]; 10

studies, 2927 women; moderate quality of evidence). Serious neonatal morbidity was similar with and without cerclage (OR 0.80 [0.55-1.18]; 6 studies, 883 women; low-quality evidence). Pregnant women with and without a cerclage were equally likely to have a healthy baby discharged home (OR 1.02 [0.97-1.06]; 4 studies, 657 women; moderate-quality evidence). Pregnant women with a cerclage were less likely to have a preterm birth compared with controls at 37 weeks, 34 weeks (mean OR 0.77 [0.66-0.89]; 9 studies, 2415 women; high-quality evidence) and 28 completed weeks pregnancy

A 2020 Cochrane review [39] presents the potential harms of cervical cerclage as including: traumatic rupture of membranes (0.4%), vaginal bleeding (1.4%), premature rupture of membranes (15.6%), preterm birth (16.4%), infection, suture slippage (1.4%), cervical dystocia (7.2%), uterine rupture (6.3%), postpartum haemorrhage (2.8%), difficulty removing the cerclage (1 %). Cerclage is associated with an increased risk of cervical rupture (from 8.9% to 25.0%), both in primiparous women (OR 3.7 [1.1-12.8]) and in repeat women (adjusted OR 12.7 [5.7-28.2]) [51].

An alternative surgical approach may be pessary placement, which has been used for over 60 years [35]. In the late 1970s, Hans Arabin developed a dome-shaped flexible silicone pessary [24], a conical ring that is inserted into the vagina until it covers the entire cervix, closing the cervical canal and preventing its dilation and/or shortening [19, 46, 74].

The PECEP (The Pesario Cervical para Evitar Prematuridad) study (2012) [43] was conducted in five hospitals in Spain and showed that cervical pessary reduces the number of preterm births up to 34 weeks in women with singleton pregnancies and a short cervix (<25 mm) (6% vs. 27%, OR 0.18 [0.08-0.37]; $p < 0.0001$). Overall neonatal morbidity did not differ between the two groups (RR 0.64 [0.27-1.50]). In the PECEP arm, the investigators decided to stop recruitment and report the results of their interim analysis.

K. H. Nicolaides et al. (2016) [60] randomized 935 women with singleton pregnancies to either cervical pessary or wait-and-see tactics. The authors found no differences in the rates of preterm birth up to 34 weeks (OR 1.12 [0.75-1.69]) [11]. The average gestational age at randomization was higher in this study (23 weeks + 5 days) compared to the study by M. Goya et al. (2012) [43] (22 weeks + 3 days), and this may have influenced the pessary effect.

In a smaller Chinese trial (n=108) that ended prematurely due to slow recruitment and new published results, delivery before 34 weeks occurred in 9.4% in the pessary group and 5.5% in the wait-and-see group, respectively ($p = 0,46$) [46].

L. Dugoff et al. (2018) conducted an open multicentre randomized controlled trial (RCT) of asymptomatic women with a gestational age of 18 weeks + 0 days to 23 weeks + 6 days, cervical length < 25 mm on transvaginal ultrasound and no previous spontaneous preterm birth. Subjects were randomized to groups with Bioteque pessary or no pessary. Vaginal progesterone was recommended for women with a cervix length ≤ 20 mm. There were no significant differences between the pessary and non-pessary groups in the rate of spontaneous preterm delivery < 37 weeks (43 vs. 40%; RR 1.09 [0.71-1.68]), spontaneous preterm delivery < 34 weeks and < 28 weeks, gestational age at delivery, birth weight, and incidence of adverse outcomes in newborns. The authors concluded that in women with a singleton pregnancy and a short cervix, without previous spontaneous preterm birth, the introduction of the Bioteque pessary does not reliably reduce the rate of preterm birth.

In the HOUSSAY (Health Outcomes and Systematic Analyses) meta-analysis, F. R. Pérez-Lopez et al. (2019) [66] searched PubMed-Medline, Embase, Scopus, Web of Science, and the Cochrane Library, as well as clinical trial registries for RCTs published in all languages from inception to July 28, 2018. Inclusion criteria were registered RCTs of singleton pregnancies with a short cervix (≤ 25 mm), measured at 22-24 weeks' gestation, comparing

the use of a cervical pessary with controls regarding the risk of spontaneous preterm birth. Three RCTs involving a total of 1,612 pregnancies (805 women using a cervical pessary) were selected and analyzed. The risk of preterm birth at < 37 weeks' gestation was lower for participants using a pessary (OR 0.46 [0.28-0.77]). The use of a pessary was associated with a higher risk of vaginal discharge (OR 2.05 [1.82-2.31]). There were no significant differences between pessary users and controls in terms of preterm birth at < 28 and < 34 weeks' gestation; average gestational age and weight of babies at birth; and in the risks of chorioamnionitis, caesarean section, and perinatal or neonatal outcomes. A subanalysis by risk of bias showed that in two RCTs with a low risk of bias, the risk of preterm birth before 34 weeks' gestation was lower in pessary users (OR 0.33 [0.16-0.66]).

R.C. Pacagnella et al. (2019) [49] showed that the combination of progesterone and pessary is common in clinical practice, but only a few studies have examined this relationship [40, 83]. N. Stricker et al. (2019) [78] attempted to compare at-risk and screening patients who received a cervical pessary alone with patients who received a pessary plus vaginal progesterone. Delivery at less than 34 weeks' gestation occurred in 17 of 53 patients (32.1%) who received a pessary plus progesterone compared with 13 of 53 patients (24.5%) who received a pessary alone ($P = 0.57$). Similarly, there was no difference in the rate of preterm birth at <28, <32, or <37 weeks' gestation. The overall poor neonatal outcome was 15.1% in the pessary group versus 18.9% in the combination group ($P = 0.96$). Median length of stay was 46.5 days (range, 9-130 days) in the combination group versus 52.0 days (range, 3-151 days) in the pessary group ($P < 0.001$).

In 2022, R.C. Pacagnella et al. [65] published the results of a Brazilian multicentre, open-label RCT in 17 perinatal centres. Asymptomatic women with a singleton or twin pregnancy and a cervical length of 30 mm or less measured at 18 0/7 to 22 6/7 weeks' gestation were randomized to cervical pessary plus vaginal

progesterone (pessary plus progesterone group) or vaginal progesterone alone versus progesterone alone) (200 mg/day). Treatment was used from randomization to 36 weeks of pregnancy or delivery. The primary outcome was a composite of neonatal mortality and morbidity. Secondary outcomes were delivery before 37 weeks and before 34 weeks of gestation. 8,168 women were studied, of whom 475 were randomized to pessary plus vaginal progesterone and 461 to progesterone alone. A complicated perinatal outcome occurred in 19.2% (89/463) of women in the pessary plus vaginal progesterone group compared with 20.9% (91/436) of women in the progesterone-only group (adjusted relative risk ratio [aRRR] 0.88 [0.69-1.12]). The frequency of delivery before 37 weeks of pregnancy was 29.1% compared to 31.4% (aRRR 0.86 [0.72-1.04]); the rate of delivery before 34 weeks was 9.9% compared with 13.9% (aRRR 0.66 [0.47-0.93]). Women in the pessary plus vaginal progesterone group had more vaginal discharge (51.6% [245/476] vs. 25.4% [117/479] [P<0.001]), pain (33.1% [157/476] vs. 24.1% [111/479] [P=0.002]) and vaginal bleeding (9.7% [46/476] vs. 4.8% [22/479] [P=0.004]). The authors concluded that in asymptomatic women with a short cervix, the combination of a pessary and progesterone did not reduce neonatal morbidity or mortality compared with progesterone alone.

Thus, treatment of CI with both a pessary and progesterone may be beneficial in reducing the incidence of preterm birth. Both interventions have been shown to be safe and reliable. However, the combination of progesterone and pessary for the prevention of CI still needs to be studied. The combination of two methods can act in both ways to prevent preterm birth: biochemical and mechanical, which makes combined treatment more effective than treatment with only one method, affecting a wider group of women at risk of CI [78]. Only a few studies are devoted to the use of sublingual tablet form of micronized progesterone in CI. When analysing the effectiveness of vaginal forms of progesterone,

the effects of the use of soft gelatine capsules or progesterone gel were mainly evaluated. There are no data on the comparison of the combined methods of using a pessary and different forms of tableted micronized progesterone, which requires further search for a solution to the problem of CI correction.

The purpose of the study was to conduct a comparative assessment of the effectiveness of the combined method of correcting isthmic-cervical insufficiency using Dr. Arabin's perforated silicone obstetric pessary and various forms of tableted micronized progesterone - vaginal and sublingual.

Material and Methods

A simple, open, prospective, randomized study was conducted, approved by the ethics committee of Odesa National Medical University in 2017 and conducted in accordance with the principles of the Declaration of Helsinki. The study was conducted in the period from 2017 to 2022 at the bases of the Communal non-profit enterprise Maternity Hospital No. 7 of Odesa City Council, LLC Reproductive Medicine Clinic Nadiya Odesa, LLC Gameta Reproductive Health Medical Center and LLC Profile Hospital AIRMED of Odesa, the Communal non-profit enterprise Regional Intensive Care Hospital of Mariupol. 215 pregnant women with CI were selected by random sampling according to the inclusion and exclusion criteria. Informed consent to participate in the study was obtained from all examined women.

The criteria for inclusion in the studied prospective groups with CI were: gestation period of 12-16 weeks, singleton pregnancy, informed voluntary consent to treatment according to the proposed method, being under supervision throughout the pregnancy. Exclusion criteria were: differentiated dysplasia of connective tissue, presence of bloody secretions from the genital tract, previous conization of the cervix, abnormalities of the structure of the uterus, multiple pregnancy, presence of uterine fibroids with a submucosal

location of the node, clinically significant causes of thyroid dysfunction before pregnancy were found, malignant diseases in the anamnesis and/or in the present, psychiatric diseases), deep vein thrombosis in the present and/or in the anamnesis, inflammatory diseases of the internal genital organs, prolapsed fetal bladder, individual intolerance of progesterone drugs.

In the main group A, 129 pregnant women with CI were included, in whom treatment and preventive measures included a combination of applying an obstetric perforated pessary by Dr. Arabin and taking a sublingual form of tableted micronized progesterone of 100 mg (2 tablets of 50 mg) three times a day until 36 weeks of pregnancy. comparison group B included 86 pregnant women who received CI treatment with an obstetric perforated pessary by Dr. Arabin and vaginal tablets of micronized progesterone 200 mg twice a day until 36 weeks of pregnancy. All women also received vitamin-mineral complexes for pregnant women, omega-3 polyunsaturated fatty acids, and magnesium supplements during the gestational period.

All pregnant women underwent a full clinical and laboratory examination in accordance with existing standards. In order to detect extragenital pathology, all women were consulted by a therapist, endocrinologist and neuropathologist.

In order to assess the state of vaginal microbiota, bacterioscopy of vaginal, cervical and urethral smears, quantitative polymerase chain reaction of scraping vaginal epithelium were performed in real time.

All pregnant women underwent transvaginal ultrasound cervicometry at 12, 14-16 and 18-20 weeks of gestation. Cervicometry was performed in accordance with the requirements

of FMF (Fetal Medicine Foundation) [19]: transvaginally; empty bladder of the patient; insertion of the sensor into the anterior vaginal vault; image of the cervical canal along its entire length - from the inner to the outer throat; the wall of the vagina was considered a sign of choosing the correct external throat; correct placement of callipers; the cervical canal is located "horizontally" on the screen; avoid compression with a sensor on the neck; avoided assessment of the length of the cervix during contraction of the uterus; a fixed image was measured after removing the sensor from the vagina; zoom of the received image, the enlarged cervix should occupy up to 2/3 of the screen area. When measuring the length of the cervix, the following rules were followed: measurement from the internal to the external throat along the endocervical canal. With a curved shape of the endocervical canal, it was measured in one of three ways: a straight segment, two segments, manual tracing along the endocervix. The length of the closed part of the cervical canal was considered the cervical length in the presence of a watering can. The closed internal opening of the cervical canal was registered as a T-shaped shape. With funnel-shaped expansion of the internal pharynx, the funnel was described as V-, Y-, and U-shaped. In the presence of a watering can, the length of the cervix had two components - the length of the watering can and the functional length, i.e. the length of the closed part of the cervical canal. To detect a hidden funnel, a funnel that hides when the walls of the uterus contract in the lower parts, a fundal test was used - compression with the sonologist's free hand in the area of the bottom of the uterus, directed downwards (Fig. 1, Fig. 2).

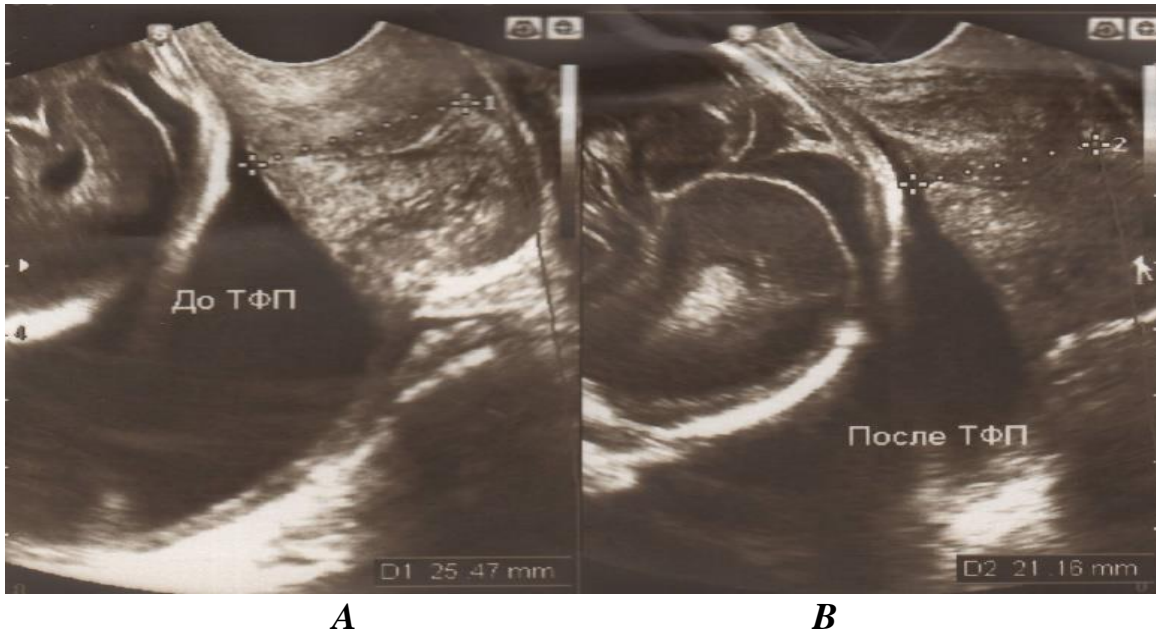


Figure 1. Vaginal cervicometry before (A) and after (B) conducting a fundal examination in a woman at 20 weeks' gestation: functional length of the cervix before the examination - 25 mm, after the examination - 21 mm, cervical width - 31 mm and 34 mm, the thickness of the lower segment is 7 mm and 7 mm, the diameter of the internal pharynx is 0 mm and 0 mm, the depth of the opening of the internal pharynx is 0 mm and 0 mm, the shape of the internal pharynx is T-shaped. An obstetric pessary was introduced at 20 weeks of pregnancy.

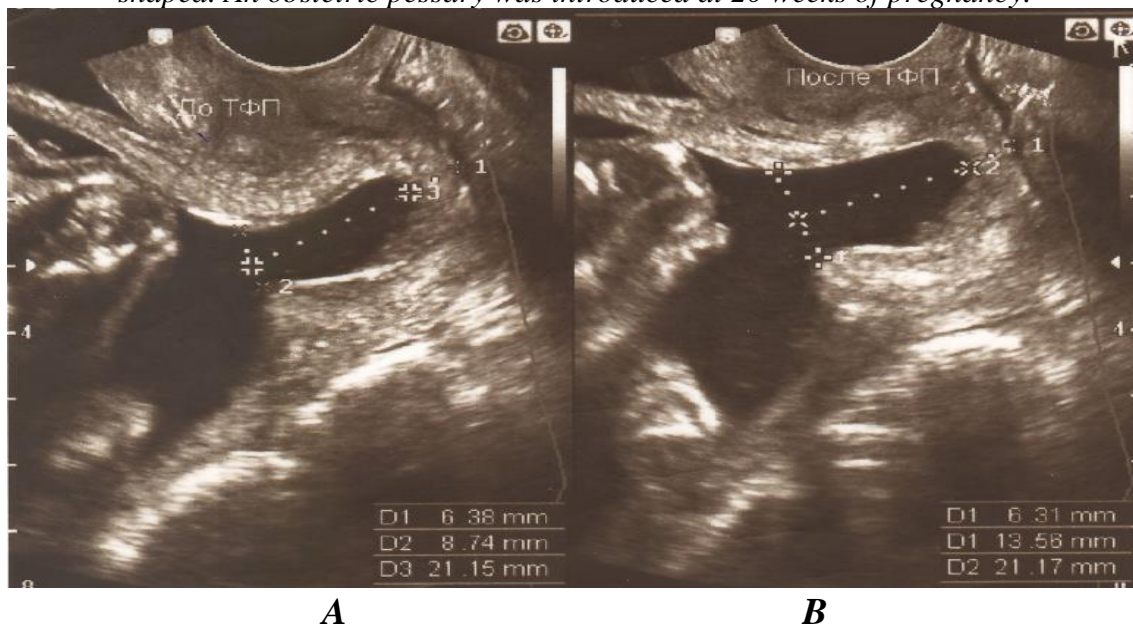


Figure 2. Vaginal cervicometry before (A) and after (B) conducting a fundus test in a pregnant woman at 18-19 weeks of gestation: functional length of the cervix before the test - 6.38 mm, after the test - 6.31 mm, cervical width - 28.11 mm and 31.12 mm, thickness of the lower segment - 6 mm and 6 mm, diameter of the internal pharynx - 8.74 mm and 13.58 mm, depth of opening of the internal pharynx - 21.15 mm and 21.17 mm, the shape of the internal pharynx is U-shaped. Dr. Arabin's obstetrical pessary was introduced at 19-20 weeks of pregnancy.

The diagnosis of CI was made on the basis of ultrasound criteria for the diagnosis of cervical obturation failure, which included the length of the cervix ≤ 25 mm, the diameter of the internal os > 6 mm, and the posterior angle of the cervix $> 90^\circ$ [8]. Arabin pessary (ARABIN® Cerclage pessary Dr. Arabin, GmbH & Co. KG, Witten, Germany) was installed in the examined patients with CI. The size of the pessary was determined according to the instructions provided by B. Arabin, Z. Alfrevic (2013) [23] and the manufacturer's recommendations. Removal of the pessary was carried out around the 37th week of pregnancy or with the beginning of regular labor. After removing the pessary, the vagina was treated with a 10% solution of povidone-iodine, and in the absence of labor, it was recommended to use a 1.5% vaginal gel in a polymer container of 5 ml containing decamethoxin 1.0 mg, sodium hyaluronate every night for 7 days - 75.0 mg, lactate buffer pH 3.8-4.5 - up to 5.0 ml.

A comparative analysis of various methods of management of pregnant women with CI was

carried out, the course of pregnancy, obstetric and perinatal consequences were evaluated.

Statistical hypothesis testing was performed using Excel with a specified critical significance level of less than or equal to 0.05. The distribution of variables was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since most variables did not follow a normal distribution, the mean (M) and error of the standard deviation (\pm SE) were calculated. Comparison of quantitative data of two independent groups was carried out using the non-parametric Mann-Whitney test. Categorical variables were assessed using Pearson's χ^2 test or Fisher's exact test.

Results

The conducted clinical and anamnestic characteristics of groups of pregnant women with CI showed their homogeneity according to such indicators as age, anthropometric data, period of taking pregnant women under observation, characteristics of menstrual function, age at the start of sexual life, reproductive history (Table 1).

Table 1. Clinical and anamnestic characteristics of the studied groups, $M \pm SE$

Indicator	Group A (n = 123) (pessary + sublingual progesterone)	Group B (n = 83) (pessary + vaginal progesterone)	p=
Age, years	30.87 \pm 0.38	31.26 \pm 0.41	0.84
Body weight, kg	56.28 \pm 0.55	57.79 \pm 0.68	0.08
Height, m	1.68 \pm 0.01	1.68 \pm 0.01	0.78
Body mass index, kg/m ²	20.04 \pm 0.25	20.67 \pm 0.32	0.13
Varge's index	1.72 \pm 0.03	1.79 \pm 0.03	0.13
Period of taking pregnant women under supervision, weeks	6.58 \pm 0.05	6.63 \pm 0.05	0.59
Menarche, years	13.05 \pm 0.09	13.12 \pm 0.13	0.67
Average duration of menstruation, days	5.28 \pm 0.11	5.47 \pm 0.14	0.30
Average duration of menstrual cycle, days	27.53 \pm 0.21	28.59 \pm 0.67	0.14
Beginning of sexual life, years	18.60 \pm 0.16	18.49 \pm 0.19	0.64
Average number of pregnancies	1.58 \pm 0.12	1.72 \pm 0.16	0.48
Average number of births	0.70 \pm 0.08	0.58 \pm 0.08	0.32
Average number of induced abortions	0.40 \pm 0.06	0.49 \pm 0.09	0.39
The average number of miscarriages	0.56 \pm 0.08	0.63 \pm 0.10	0.59

Only 25.58% of pregnant women in group A and 20.93% of women in group B had first pregnancies, 74.42% and 79.07%, respectively, had second pregnancies ($\chi^2=0.617$, $p=0.43$). Childbirth occurred in the anamnesis in the main group in 46.51% of people and in the comparison group - in 79.07% ($\chi^2=0.113$, $p=0.74$), including premature births - in 20.93% and 27.01% ($\chi^2=3.073$, $p=0.08$). Miscarriages in groups A and B were observed in 32.56% and 39.53% of cases ($\chi^2=1.099$, $p=0.29$), of which they were early in 42.86% and 47.06% of women and late in 57.14% and 52.94% ($\chi^2=0.134$, $p=0.71$).

Intrauterine interventions with dilation of the cervical canal were previously performed in 67.44% of patients of group A and 62.79% of group B ($\chi^2=0.496$, $p=0.48$). 27.91% and 20.93% of women had a history of hysteroscopy, respectively ($\chi^2=1.335$, $p=0.25$).

The studied groups were homogeneous in terms of the spectrum of gynecological diseases: ectopy of the cylindrical epithelium of the cervix (20.93% vs. 27.91%, $\chi^2=1.388$, $p=0.24$), dysplasia of the cervix (14.73% vs. 13.95%, $\chi^2=0.025$, $p=0.87$), cervical leukoplakia (2.33% vs. 5.81%, $\chi^2=1.753$, $p=0.19$), cervical polyp

(9.30% vs. 6.98%, $\chi^2=0.364$, $p=0.55$), chronic cervicitis (58.91% vs. 53.49%, $\chi^2=0.619$, $p=0.43$), bacterial vaginosis (39.53% vs. 41.86%, $\chi^2=0.116$, $p=0.73$), vaginitis (30.23% vs. 37.21%, $\chi^2=1.356$, $p=0.29$), chronic salpingo-oophoritis (18.60% vs. 20.93%, $\chi^2=0.178$, $p=0.57$).

Extragenital diseases were registered in more than half of pregnant women with CI, the most common of which were: somatoform autonomic dysfunction of the nervous system (37.21% in group A vs. 39.53% in group B, $\chi^2=0.118$, $p=0.73$), varicose disease (25.58% vs. 27.91%, $\chi^2=0.143$, $p=0.71$), chronic gastroduodenitis (20.93% vs. 27.91%, $\chi^2=0.143$, $p=0.71$), scoliosis (16.28% vs. 20.93%, $\chi^2=0.752$, $p=0.39$), biliary tract dyskinesia (11.63% vs. 16.28%, $\chi^2=0.957$, $p=0.33$).

Obstetrical pessary was introduced in examined women between 12 and 20 weeks of pregnancy, on average in group A at 17.23 ± 0.18 weeks and in group B at 17.42 ± 0.27 weeks ($p=0.57$).

The course of pregnancy in patients with CI did not differ depending on management tactics (Table 2).

Table 2. Peculiarities of the course of pregnancy in the examined groups, n (%)

Indicator	Group A (n = 123) (pessary+ sublingual progesterone)	Group B (n = 83) (pessary + vaginal progesterone)	$\chi^2=$	$p=$
Anemia	9 (6.98)	4 (4.65)	0.491	0.48
Threat of abortion	81 (62.79)	56 (65.12)	0.121	0.73
Retrochorial hematoma	18 (13.95)	10 (11.63)	0.246	0.62
Vomiting of pregnant women	3 (2.33)	4 (4.65)	0.886	0.35
Abnormal location of the placenta	42 (32.56)	26 (30.23)	0.129	0.72
Low placentation	29 (22.48)	18 (20.93)	0.073	0.79
Marginal placenta previa	10 (7.75)	6 (6.98)	0.045	0.83
Central placenta previa	3 (2.33)	2 (2.33)	0.000	1.00
Placental dysfunction	12 (9.30)	15 (17.44)	3.113	0.08
Initial cervical-vaginal dysbiosis	81 (62.79)	51 (59.30)	0.265	0.61
Preeclampsia	4 (3.10)	4 (4.65)	0.346	0.56
Oligohydramnios	0 (0.00)	2 (2.33)	3.028	0.08
Polyhydramnios	4 (3.10)	5 (5.81)	0.947	0.33

The specific weight of the complete migration of the placenta and its normal location during childbirth were in group A 40/42 (95.24%) of cases, in group B – 25/26 (96.15%), $\chi^2=0.032$, $p=0.86$.

When initial cervical-vaginal dysbiosis was detected, all pregnant women were thoroughly sanitized. Later in the course of pregnancy, recurrence of cervical-vaginal dysbiosis in group A was registered in 2/81 (2.47%) women, in group B - in 6/51 (11.76%), $\chi^2=4.750$, $p=0.03$. Additional sanitation was carried out, but in three pregnant women from group B, in connection with abundant secretions, pronounced leukocyte reaction according to the results of the examination, it was necessary to remove the pessary with further sanitation of the vagina and re-introduction of the pessary. It should be noted that 60.47% of pregnant women of group A and 67.44% of group B complained during pregnancy after pessary insertion about increased vaginal secretions,

which were not accompanied by a pronounced leukocyte reaction. In some cases, the Actim PROM test was used to determine amniotic fluid in vaginal secretions for differential diagnosis with premature rupture of membranes.

In one case in group A, an allergic reaction to the preparation of micronized progesterone was noted, which was manifested by the appearance of hives on the hands, face, and thighs of a woman.

Two women who were initially offered sublingual progesterone complained of severe nausea and were switched to vaginal progesterone.

None of the women who received vaginal or sublingual micronized progesterone for the correction of CI showed an increase in the serum levels of liver transaminases.

The results of pregnancy and childbirth were evaluated in the studied groups (Table 3).

Table 3. Results of pregnancy and childbirth depending on the method of management, n (%)

Indicator	Group A (n = 123) (pessary+ sublingual progesterone)	Group B (n = 83) (pessary + vaginal progesterone)	$\chi^2=$	p=
Premature rupture of fruit membranes	6 (4.65)	6 (6.98)	0.530	0.47
Childbirth up to 32 weeks	2 (1.55)	4 (4.65)	1.829	0.18
Childbirth at 33-36 weeks	6 (4.65)	6 (6.98)	0.530	0.47
Term delivery	121 (93.80)	76 (88.37)	1.981	0.16
Cesarean section	18 (13.95)	14 (16.28)	0.220	0.64
Postpartum bleeding	3 (2.33)	6 (6.98)	2.783	0.10
Neonatal morbidity	6 (4.65)	9 (10.47)	2.688	0.10
Weight of the child at birth < 1500 g	2 (1.55)	5 (5.81)	2.978	0.08

As can be seen from the table. 3, the studied groups had no significant differences in the frequency of premature rupture of membranes, delivery before 32 weeks, delivery at 33-36 weeks, emergency delivery, cesarean section, postpartum hemorrhage, neonatal morbidity, birth of children weighing < 1500 g. The average weight of newborns in the main group

was 3420.24 ± 48.98 g, the comparison group was 3360.23 ± 66.38 g ($p=0.47$).

When comparing the compliance of treatment and preventive measures, it was established that parturient women rated them in the group of obstetric pessary + sublingual progesterone as 9.19 ± 0.11 points, in the group of obstetric

pessary + vaginal progesterone as 7.83 ± 0.17 points ($p < 0.01$).

Discussion

Preterm birth is a major cause of perinatal morbidity and mortality. About 15 million babies worldwide were born prematurely in 2015, causing 1.1 million deaths and short- and long-term disability in those who survived [33]. Despite numerous studies on the diagnosis, prevention and treatment of premature births, their frequency does not tend to decrease, and in a number of countries, on the contrary, their increase is noted [70].

One of the main reasons for termination of pregnancy in the second - at the beginning of the third trimester is CI [69]. This problem has an important medical, social and economic significance [57].

According to the conclusions of the RCT, there is no convincing data in favor of any of the proposed methods of correction of CI [1, 77]. We made an attempt to compare two combined methods of CI correction - the placement of an obstetric pessary in combination with sublingual or vaginal tablet progesterone.

An obstetric pessary is a silicone device used to prevent involuntary premature birth. The main hypotheses about the mechanism of its action are that the pessary helps to keep the cervix closed and changes the slope of the cervical canal so that the mass of the pregnant uterus is not directly above the internal opening. Another proposed mechanism is that the pessary may strengthen the immunological barrier between the chorioamnion and the vaginal microbiological flora. Thus, the maximum pressure of the fetus and extraembryonic structures is redistributed from the region of the failed cervix to the front lower segment of the uterus that is being formed. The formation of a sharper uterine-cervical angle during correction of the cervix with a pessary was confirmed by magnetic resonance imaging data. This angle is preserved with the correct placement of the pessary on the cervix [30, 37].

Redistribution of pressure from the cervix under the influence of a pessary leads to a decrease in Ferguson's reflex. Ferguson's reflex is a neuroendocrine reflex that occurs when pressure on the cervix is increased by a growing fetus, while it stretches and stimulates nerve endings. As a result, oxytocin is released in the hypothalamic-pituitary system, which in turn increases the tone of the myometrium and further increases the pressure on the cervix [7]. Due to the closing function of the pessary, a mucous plug is preserved in the cervical canal, which prevents the ascending path of infection [7, 22, 30].

The method of introducing an obstetric pessary is non-invasive, does not require special training and the participation of related specialists (anesthesiologist), causes less psychological trauma compared to cerclage. One of the main advantages of this method is the possibility of its successful application at the stage of preclinical manifestations of CI (according to ultrasound data, anamnesis, presence of risk factors) and its prophylactic effect, as well as the possibility of its use in outpatient settings [6].

We associate the high numbers of pregnancy results obtained in examined women with CI with the earliest possible introduction of a pessary and the appointment of effective doses of the most bioavailable micronized progesterone, and we believe that the timeliness of treatment and preventive measures plays the most important role in the successful correction of CI.

It is interesting to note that the specific weight of the complete migration of the placenta, its displacement up to the bottom of the uterus together with the formation of the lower segment when using the obstetric pessary of Dr. Arabin and its normal location during childbirth accounted for more than 95% of cases in both studied groups among women with the initial anomalous location of the placenta at the beginning of the second trimester due to a change in the uterine-cervical angle and a decrease in direct pressure on the internal opening of the cervix, which coincides with the data of I.V. Shamina et al. (2018) [16].

More than 60% of pregnant women in the examination groups complained of an increase in vaginal secretions during pregnancy after pessary placement. The detected hypersecretion of the vaginal glands against the background of the pessary was probably due to an increase in the secretory activity of the glands and was not associated with an increase in infection. The results obtained in the conducted study do not contradict the data previously obtained by other researchers [4, 16, 22, 43, 52], who also noted an increase in vaginal secretion against the background of the pessary, which is not related to the presence of infection.

The choice of vaginal tableted micronized progesterone (Luteina, Adamed, Poland) during the study was made in connection with the creation of a high and stable physiological concentration of the active substance in the blood plasma after the use of this drug in low doses. Of course, the higher the concentration of progesterone in the plasma after intravaginal administration, the higher it is in the target organ as well [10].

When using vaginal forms of progesterone, the so-called effect of the first passage through the uterus occurs. Thanks to this, progesterone directly affects the target organ - the uterus and its cervix. The most important feature of the vaginal form of progesterone is the absence of the effect of passing through the liver, which reduces the risk of side effects and at the same time increases the effectiveness of such pharmacotherapy [10]. None of the examined women had an increase in the level of liver transaminases above normal.

It is known that the auxiliary composition and production technology of Lutein tablets contribute to increasing the therapeutic effectiveness of the main components of the drug, ensuring their maximum contact with the vaginal mucosa and a sufficient duration of their presence in the uterine cavity with the minimization of mucosal irritation. The compact oblong-flat shape of the tablet increases the area of contact with the mucous membrane - it is conveniently located in the vagina, minimizing the feeling of a foreign body

inside. The tablet has a smooth glossy surface and rounded edges, slides after introduction, without irritating the mucous membrane of the vagina. The tablet does not disintegrate upon contact with the glandular secretion of the vagina, but begins to slowly dissolve layer by layer, which is due to its special structure. In particular, at the initial stage of vaginal tablet production, two-level granules containing active substances are formed; granules are strictly calibrated by size, after which they are coated with a special mixture that creates the structure of a matrix tablet: granules of active substances are held together by binding "bridges", which in a moist environment begin to gradually (layer by layer) dissolve [10].

In the research of V. D. Lukyanchuk and O. V. Kuznetsova (2016) [9] it was established that Luteina tablets for vaginal use have a high degree of solubility. The authors showed that in an environment close to vaginal, with a pH of 4.5 ± 0.5 and a temperature of 37 ± 0.5 °C, the tablet dissolves within 5 minutes. During this time, an active substance is released that ensures a high level of progesterone bioavailability.

Luteina vaginal tablets contain citric acid monohydrate as an additional component, which supports the physiological pH of the vaginal environment and the colonization resistance of the cervico-vaginal microbiota. Thanks to this, the acidity of the vaginal environment does not change, which is especially important for such a common pathology as bacterial vaginosis [10]. With this, we associate the low rate of recurrences of cervical-vaginal dysbiosis when using a combination of an obstetric pessary and vaginal tablets of micronized progesterone and Luteina. The sublingual form of tableted micronized progesterone (Luteina, Adamed, Poland) when taken in a dose of 100 mg is more effective in terms of the parameters of the peak concentration in the blood serum and the time of creation of the effective concentration ($C_{max} 17.6 \pm 3.8$ ng/ml, the time of creation of the effective concentration $t - 30-60$ min.) in comparison with vaginal (tablets and capsules) dosage forms ($C_{max} 10.9 \pm 4.2$ ng/ml, $t - 6-7$ h

and C_{max} 9.7 ng/ml, $t - 1-3$ h, respectively) in the same dosage. When comparing the enteral form of micronized progesterone in a dose of 200 mg (C_{max} 4.3-11.7 ng/ml, $t - 2$ h), the advantage of the sublingual form of the Lutein preparation in terms of time of creation and level of peak concentration is also noted. A comparison of the above-described parameters when using the sublingual form (C_{max} 17.6 ± 3.8 ng/ml) of micronized progesterone and the intramuscular injection of an oil solution (C_{max} 14.3 ng/ml) also revealed the advantages of the sublingual form [11]. Some works also show that peak plasma concentrations are reached after 30 minutes. and stored for 4 hours. after oral administration of the sublingual form in the range from 8.5 to 70.6 ng/ml, while after vaginal administration peak levels of concentration are reached within 8 hours. at the level of 4.4-181.1 ng/ml, which indicates the superiority of sublingual administration in terms of the time of onset of the effect and the duration of its development [53, 62]. The given data indicate the high bioavailability of the sublingual form of Luteina, minimal complications associated with metabolism in the liver, and the possibility of reducing hepatotoxicity during treatment. The sublingual route of administration has the advantages of oral and parenteral administration - high adherence to treatment, absence of passage through the digestive tract and independence of the effect from the morphofunctional features of the digestive tract, stomach filling, features of intestinal blood circulation, etc., high concentration of the drug in the blood [13, 18]. Our study showed that the use of both vaginal and sublingual tableted micronized progesterone in combination with the application of Dr. Arabin's obstetric perforated pessary has equal effectiveness in correcting CI

with regard to obstetric and perinatal outcomes. Indicators of neonatal morbidity and the number of newborns with a weight of less than 1500 g did not have significant differences depending on the type of CI correction. The significant advantages of using the sublingual form of tableted micronized progesterone in the combined technique of CI correction were greater compliance, ease of use and probably lower frequency of recurrences of cervical-vaginal dysbiosis.

Conclusion

Combined methods of CI correction using Dr. Arabin's vaginal perforated obstetric pessary in combination with tableted micronized progesterone are effective and safe when using both vaginal and sublingual forms of progesterone, but the method of using a pessary and sublingual progesterone is more optimal, convenient and compliant. Both techniques can be widely used in clinical practice.

Authors Contributions

Authors declare about equal contribution.

Funding

This study had was not funded from outside.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Odessa National medical University (7/119/2018, 27 December 2018).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Belotserkovtseva, LD, Kovalenko, LV, Mirzoeva, GT. "Risk factors for the formation of isthmio-cervical insufficiency leading to premature birth." *Bulletin of SurSU. The medicine.* 2(20) (2014):26-30.
2. Bepalova, ON, Sargsyan, GS. "Choice of method for correction of isthmio-cervical insufficiency." *Journal of Obstetrics and Women's Diseases.* 66;3 (2017):157–168.
3. Bulanov, MN. "Ultrasound diagnosis of diseases of the cervix. Guide for doctors." Moscow: Vidar-M; (2017). 304 p.
4. Egorova, YaA, Rybalka, AN. "Unloading obstetric pessary as an addition to the treatment of isthmio-cervical insufficiency." *Crimean Journal of Experimental and Clinical Medicine.* 2;14 (2014):17-21.
5. Zhabchenko, IA. "Obstetric tactics in isthmio-cervical insufficiency: the solution of the main and related problems." *Protection of motherhood and childhood.* 1(25) (2015):58-65.
6. Zhabchenko, IA, Oleshko, VF. "Algorithm of obstetric actions in isthmio-cervical insufficiency." *Women's health.* 6 (102) (2015):76–78.
7. Kaplan, YuD, Zakharenkova, TN, Zhuravlev, AYu. "The role of transvaginal ultrasound as a control method for conservative correction of a short cervix with a cervical pessary. reproductive health." *Eastern Europe.* 7(2) (2017):195-204.
8. Kaplan, YUD, Zakharenkova, TN. "Comparative analysis of methods for diagnosing the state of the cervix during pregnancy." *Problems of health and ecology.* 1(51) (2017):6-13.
9. Lukyanchuk, VD, Kuznetsova, OV. "In vitro study of drug solubility in solid dosage form for intravaginal administration." *Medical aspects of a woman's health.* 1 (97) (2016):2-5.
10. Opryshko, VI, Nosivets, DS. "Innovations and trends in the clinical pharmacology of vaginal forms of gestagens." *Medical aspects of women's health.* 5(102) (2016):55-61.
11. Opryshko, VI, Nosivets, DS. "Sublingual form of progesterone: the need for innovation or the challenges of modern medicine." *Women's health.* 10(106) (2015):37-42.
12. Safonova, IN. "High-risk pregnancy: sonographic monitoring." Kyiv: Medicine of Ukraine; (2019). 246 p. ISBN 978-617-7769-01-8.
13. Khomyak, NV, Mamchur, VY, Khomyak, EV. "Clinical and pharmacological features of dosage forms of micronized progesterone used during pregnancy." *Medical aspects of women's health.* 2(88) (2015):28-35.
14. Tetrushvili, NK, Agadzhanova, AA, Milusheva, AK. "Isthmio-cervical insufficiency with prolapsed membranes: new treatment options." *Medical advice. Gynecology.* (2015):50-2.
15. Zvignun, MV. "Failure to bear a pregnancy is one of the consequences of surgical interventions on the cervix in women of reproductive age." *Women's health.* 8 (94) (2014):44-46.
16. Shamina, IV, Tirskaia, YuI, Lazareva, OV et al. "Prevention of preterm birth in high-risk pregnant women by using Dr. Arabin's obstetric pessary." *Siberian Medical Review.* 1 (2018):59-65.
17. Shcherbina, MO, Muawiya Salem Nasser Almaradat. "New ways to optimize the management of women with ischemic-cervical insufficiency." *Collection of scientific papers of the Association of Obstetricians and Gynecologists of Ukraine.* Kyiv: Polygraph Plus. (2014): 315-317.
18. Shurpyak, SA. "Modern forms of natural progesterone with different routes of administration in the treatment of threatened abortions and prevention of preterm birth. Literature review." *Women's health.* 10(86) (2013):2-7.
19. Abdel-Aleem, H, Shaaban, OM, Abdel-Aleem, MA. "Cervical pessary for preventing preterm birth." *Cochrane Database Syst Rev.* 31(5) (2013):CD007873.

-
20. Alfirevic, Z, Stampalija, T, Medley, N. "Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy." *Cochrane Database Syst Rev.* 2017(6) (2017): CD008991.
 21. Allen, KG, Harris, MA. "The role of n-3 fatty acids in gestation and parturition." *Exp Biol Med (Maywood).* 226(6) (2001):498-506.
 22. Arabin, B, Halbesma, JR, Vork, F, et al. "Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix?" *Journal of Perinatal Medicine.* 31(2) (2003):122-33.
 23. Arabin, B, Alfirevic, Z. "Cervical pessaries for prevention of spontaneous preterm birth: past, present and future." *Ultrasound Obstet Gynecol.* 42 (2013):390–399.
 24. Arabin, H. "Pessartherapie (therapy with pessaries)". New York (NY): Thieme; (1991). pp. 263–276.
 25. Barinov, SV, Artymuk, NV, Novikova, ON, et al. "Analysis of risk factors and predictors of pregnancy loss and strategies for the management of cervical insufficiency in pregnant women at a high risk of preterm birth." *J Matern Fetal Neonatal Med.* 34(13) (2021):2071-2079.
 26. Berghella, V, Seibel-Seamon, J. "Contemporary use of cervical cerclage." *Clin Obstet Gynecol.* 50(2) (2007):468–477.
 27. Boelig, RC, Berghella, V. "Current options for mechanical prevention of preterm birth." *Semin Perinatol.* 41(8) (2017):452-460.
 28. Bortoletto, TG, Silva, TV, Borovac-Pinheiro, A et al. "Cervical length varies considering different populations and gestational outcomes: Results from a systematic review and meta-analysis." *PLoS One.* 16(2) (2021): e0245746.
 29. Brown, R, Gagnon, R, Delisle, MF. "No. 373-Cervical Insufficiency and Cervical Cerclage." *J Obstet Gynaecol Can.* 41(2) (2019):233-247.
 30. Cannie, M, Dobrescu, O, Gucciardo, L et al. "Arabin cervical pessary in women at high risk of preterm birth: a magnetic resonance imaging observational follow-up study." *Ultrasound Obstet Gynecol.* 42(4) (2013):426-33.
 31. Carbonne, B, Dallot, E, Haddad, B et al. "Effects of progesterone on prostaglandin E(2)-induced changes in glycosaminoglycan synthesis by human cervical fibroblasts in culture." *Mol Hum Reprod.* 6(7) (2000):661-4.
 32. Chan, YY, Jayaprakasan, K, Tan, A et al. "Reproductive outcomes in women with congenital uterine anomalies: a systematic review." *Ultrasound Obstet Gynecol.* 38(4) (2011):371-82.
 33. Chawanpaiboon, S, Vogel, JP, Moller, AB et al. "Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis." *Lancet Glob Health.* 2019 Jan;7(1) (2019): e37-e46.
 34. Committee on Practice Bulletins-Obstetrics, The American College of Obstetricians and Gynecologists. "Practice bulletin no. 130: prediction and prevention of preterm birth." *Obstet Gynecol.* 120(4) (2012):964-73.
 35. Cross, RG. "Treatment of habitual abortion due to cervical incompetence." *Lancet.* 274 (1959):127.
 36. Cruz-Melguizo, S, San-Frutos, L, Martínez-Payo, C et al. "Cervical pessary compared with vaginal progesterone for preventing early preterm birth: a randomized controlled trial." *Obstet Gynecol.* 132(4) (2018):907-915.
 37. Driggers, R. "Prevention of preterm birth - what works and what doesn't?" *Obstet Gynecol Int J.* 2(5) (2015):179-182.
 38. Dugoff, L, Berghella, V, Sehdev, H et al. "Prevention of preterm birth with pessary in singletons (PoPPS): randomized controlled trial." *Ultrasound Obstet Gynecol.* 51 (2018): 573-579.

-
39. Eleje, GU, Ek, AC, Ikechebel, JI et al. "Cervical stitch (cerclage) in combination with other treatments for preventing spontaneous preterm birth in singleton pregnancies." *Cochrane Database Syst Rev.*;9(9) (2020):CD012871.
 40. Fox, NS, Gupta, S, Lam-Rachlin, J et al. "Cervical pessary and vaginal progesterone in twin pregnancies with a short cervix." *Obstet Gynecol.* 127(2016):625–30.
 41. Gernand, AD, Schulze, KJ, Stewart, CP et al. "Micronutrient deficiencies in pregnancy worldwide: health effects and prevention." *Nat Rev Endocrinol.* 12(5) (2016):274-89.
 42. Gonzales, SK, Adair, CD, Torres, C et al. "Robotic-Assisted Laparoscopic Abdominal Cerclage Placement During Pregnancy." *J Minim Invasive Gynecol.* 25(5) (2018):832-835.
 43. 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.* 379(9828) (2012):1800–1806.
 44. Hassan, SS, Romero, R, Vidyadhari, D, et al. "Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.*" 38(1) (2011):18-31.
 45. House, M, Tadesse-Telila, S, Norwitz, ER et al. "Inhibitory effect of progesterone on cervical tissue formation in a three-dimensional culture system with human cervical fibroblasts." *Biol Reprod.* 90(1) (2014):18.
 46. Hui, SYA, Chor, CM, Lau, TK et al. "Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial." *Am J Perinatol.* 30(4) (2013):283-8.
 47. Iams, JD, Goldenberg, RL, Meis, PJ, et al. "The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network." *N Engl J Med.* 334(9) (1999):567-72.
 48. Karbasian, N, Sheikh, M, Pirjani R, et al. "Combined treatment with cervical pessary and vaginal progesterone for the prevention of preterm birth: A randomized clinical trial." *J Obstet Gynaecol Res.* 42(12) (2016):1673-1679.
 49. Keelan, JA, Newnham, JP. "Recent advances in the prevention of preterm birth." *F1000Res.* 1 (2017):6.
 50. Koullali, B, van Kempen, LEM, van Zijl, MD et al. "A multi-centre, non-inferiority, randomised controlled trial to compare a cervical pessary with a cervical cerclage in the prevention of preterm delivery in women with short cervical length and a history of preterm birth - PC study." *BMC Pregnancy Childbirth.* 17(1) (2017):215.
 51. Landy, HJ, Laughon, SK, Bailit, JL et al. "Characteristics associated with severe perineal and cervical lacerations during vaginal delivery." *Obstet Gynecol.* 117(3) (2011):627–35.
 52. Liem, SMS, van Pampus, MG, Mol, BWJ et al. "Cervical Pessaries for the Prevention of Preterm Birth: A Systematic Review." *Obstetrics and Gynecology International.* 2013 (2013):1-10.
 53. Maxson, WS, Hargrove, JT. "Bioavailability of oral micronized progesterone." *Fertil Steril.* 44(5) (1985):622-6.
 54. Mahendroo, M. "Cervical remodeling in term and preterm birth: insights from an animal model." *Reproduction.* 143(4) (2012):429-38.
 55. Mahendroo, MS, Porter, A, Russell, DW et al. "The parturition defect in steroid 5 α -reductase type 1 knockout mice is due to impaired cervical ripening." *Mol Endocrinol.* 13(6) (1999):981-92.
 56. McDonald, IA. "Suture of the cervix for inevitable miscarriage. *Journal of Obstetrics and Gynaecology of the British Commonwealth.*" 64(3) (1957):346-50.

-
57. Medley, N, Poljak, B, Mammarella, S, Alfirevic Z. “Clinical guidelines for prevention and management of preterm birth: a systematic review.” *BJOG*. 125(11) (2018):1361-1369.
 58. Mönckeberg, M, Valdés, R, Kusanovic, JP et al. “Patients with acute cervical insufficiency without intra-amniotic infection/inflammation treated with cerclage have a good prognosis.” *J Perinat Med*. 47(5) (2019):500-509.
 59. Nicolaides, KH, Syngelaki, A, Poon, LC et al. “Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial.” *Am J Obstet Gynecol*. 214(1) (2016):3. e1-9.
 60. Nicolaides, KH, Syngelaki, A, Poon, LC et al. “A Randomized Trial of a Cervical Pessary to Prevent Preterm Singleton Birth.” *N Engl J Med*. 374(11) (2016):1044–1052.
 61. Nold, C, Maubert, M, Anton, L et al. “Prevention of preterm birth by progesterone agents: what are the molecular mechanisms?” *Am J Obstet Gynecol*. 208(3) (2013):223. e1-7.
 62. Norman, TR, Morse, CA, Dennerstein, L. “Comparative bioavailability of orally and vaginally administered progesterone.” *Fertil Steril*. 56(6) (1991):1034-9.
 63. Olsen, SF, Østerdal, ML, Salvig, JD et al. “Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil.” *Eur J Clin Nutr*. 61(8) (2007):976-85.
 64. Pacagnella, RC, Mol, BW, Borovac-Pinheiro, A et al. “A randomized controlled trial on the use of pessary plus progesterone to prevent preterm birth in women with short cervical length (P5 trial).” *BMC Pregnancy Childbirth*. 19(1) (2019):442.
 65. Pacagnella, RC, Silva, TV, Cecatti, JG, et al. “Pessary Plus Progesterone to Prevent Preterm Birth in Women With Short Cervixes: A Randomized Controlled Trial. *Obstet Gynecol*.” 139(1) (2022):41-51.
 66. Pérez-López, FR, Chedraui, P, Pérez-Roncero, GR et al. “Health Outcomes and Systematic Analyses (HOUSSAY) Project. Effectiveness of the cervical pessary for the prevention of preterm birth in singleton pregnancies with a short cervix: a meta-analysis of randomized trials.” *Arch Gynecol Obstet*. 299(5) (2019):1215-1231.
 67. Rådestad, A, Christensen, NJ, Strömberg, L. “Induced cervical ripening with Mifepristone in first trimester abortion. A double-blind randomized biomechanical study.” *Contraception*. 38(3) (1988):301–12.
 68. Resnik, R, Lockwood, Ch, Moore, Th et al. “Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice.” 8th Edition. Elsevier; (2018). 1408 p.
 69. Rios, JD, Shah, PS, Beltempo, M et al. “Costs of Neonatal Intensive Care for Canadian Infants with Preterm Birth.” *J Pediatr*. (229 2021):161-167.e12.
 70. Romero, R, Conde-Agudelo, A, Da Fonseca, E et al. “Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data.” *Am J Obstet Gynecol*. 218(2) (2018):161-180.
 71. Romero, R, Nicolaides, K, Conde-Agudelo, A et al. “Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data.” *Am J Obstet Gynecol*. 206(2) (2012):124.e121-119.
 72. Saccone, G, Berghella, V. “Omega-3 long chain polyunsaturated fatty acids to prevent preterm birth: a systematic review and meta-analysis.” *Obstet Gynecol*. 2015 Mar;125(3):663-672
 73. Saccone, G, Berghella, V. “Omega-3 supplementation to prevent recurrent preterm birth: a systematic review and metaanalysis of randomized controlled trials.” *Am J Obstet Gynecol*. 213(2) (2015):135-40.

-
74. Saccone, G, Maruotti, GM, Giudicepietro, A et al. "Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial." *JAMA*. 318(23) (2017):2317-2324.
 75. Shirodkar, VN. "A new method of operative treatment for habitual abortions in the second trimester of pregnancy." *Antiseptic*. 52(1955):299-300.
 76. Society for Maternal and Fetal Medicine (accessed on December 31, 2017)
 77. Stadnick, NA, Sadler, E, Sandall, J et al. "Comparative case studies in integrated care implementation from across the globe: a quest for action." *BMC Health Serv Res*. 19(1) (2019):899.
 78. Stricker, N, Timmesfeld, N, Kyvernitakis, I et al. "Vaginal progesterone combined with cervical pessary: a chance for pregnancies at risk for preterm birth?" *Am J Obstet Gynecol*. 214 (2016):739. e1-739.e10.
 79. Suhag, A, Berghella, V. "Cervical cerclage. *Clin Obstet Gynecol*." 57(3)(2014):557-67.
 80. Thakur, M, Mahajan, K. "Cervical Incompetence. *StatPearls [Internet]*." Treasure Island (FL): StatPearls Publishing; (2019) Dec 9.
 81. Tyan, P, Mourad, J, Wright, B et al. "Robot-assisted transabdominal cerclage for the prevention of preterm birth: A multicenter experience." *Eur J Obstet Gynecol Reprod Biol*. 232 (2019):70-74.
 82. Vink, J, Myers, K. "Cervical alterations in pregnancy." *Best Pract Res Clin Obstet Gynaecol*. 52 (2018):88-102.
 83. 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*. 188 (2015):129-32.
 84. Wang, HL, Yang, Z, Shen, Y et al. "Clinical outcome of therapeutic cervical cerclage in short cervix syndrome." *Zhonghua Fu Chan Ke Za Zhi*. 53(1) (2018):43-46.
 85. Wei, M, Jin, X, Li, TC et al. "A comparison of pregnancy outcome of modified transvaginal cervicoisthmic cerclage performed prior to and during pregnancy." *Arch Gynecol Obstet*. 297(3) (2018):645-652.
 86. Wing, DA, Fassett, MJ, Mishell, DR. "Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial." *Obstet Gynecol*. 96(4) (2000):543-8.
 87. Word, RA, Li, XH, Hnat, M, Carrick, K. "Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts." *Semin Reprod Med*. 25(1) (2007):69-79.
 88. Zheng, L, Dong, J, Dai, Y et al. "Cervical pessaries for the prevention of preterm birth: a systematic review and meta-analysis." *J Matern Fetal Neonatal Med*. 32(10) (2019):1654-1663.
 89. Zimmerman, AL, Neeman, O, Wiener, Y et al. "First year experience using arabin cervical pessary with intravaginal micronized progesterone for the prevention of preterm birth in patients with mid-trimester short cervix." *Harefuah*. 153(2) (2014):79-82.