

## Research Article

# Use of Noninvasive Cerclage in Combination of Micronized Progesterone in Miscarriage Of Multifetal Pregnancy

Iryna Nikitina<sup>1\*</sup>, Alla Boychuk<sup>2</sup>, Valentina Kondratiuk<sup>3</sup>, Tatyana Babar<sup>1</sup>

## Abstract

We represent the results of the combined method of treatment and prevention of miscarriage in women with a multiple pregnancy and a high risk of the threat of termination the pregnancy because of using the obstetric unloading pessaries, combined with micronized progesterone. The efficiency of this method of treatment is evidenced by the rapid elimination of clinical symptoms of threatened abortion, accelerating the regression of ultrasound markers, reducing the number of complications in of pregnant women and reducing the time of their stay in hospital.

**Goal:** To evaluate the effectiveness of the handling the obstetric pessary in combination with micronized progesterone at women with multifetal pregnancy and a high risk of miscarriage.

**Materials and methods.** We analyzed 120 cases of multifetal pregnancies with signs of miscarriage within the terms from 16 to 28 weeks. The first group of the examined women was: 40 pregnant women with twins and signs of miscarriage, who in the scheme of treatment and prophylactic measures were offered to use the unloading obstetric pessaries in combination with continuous therapy by natural micronized progesterone until 36 weeks of pregnancy. The second group included 40 pregnant women with twins, who were laid seam on the cervix because of istmicocervical insufficiency and were applied short-term courses of therapy by gestagens. The control group comprised 40 pregnant women with twins at the age of 16-28 weeks of pregnancy who were conducted the therapy about the threat of miscarriage according to the current clinical protocols (Order of the Ministry of Health of Ukraine No. 624). It was carried out the analysis of the course of pregnancy, childbirth, the postpartum period and the state of neonatal adaptation in the surveyed groups.

**Results.** In the first group, urgent childbirth occurred in 34 (85%) cases, in group II in 29 (72.5%) cases, in control group – in 25 (62.5%) cases. Cesarean delivery was performed in 7 (17.5%) patients of group I pregnant women, in 9 (22.5%) of group II patients and in 11 (27.5%) in the pregnant group. When studying the state of neonatal adaptation of newborns in the examined groups, the following results were obtained. The average weight of the newborns in group I was  $3245 \pm 280$  g, in group II  $2865 \pm 365$  g, in the control group -  $2975 \pm 325$  g ( $p > 0.05$ ). The evaluation of the state of newborns on the Apgar scale, respectively at the 1st and 5th minutes, was respectively: in newborns of the I group,  $7.5 \pm 1.4$  and  $8.4 \pm 1.3$  points, in group II -  $7.3 \pm 1.6$  and  $8.2 \pm 1.1$  points, in the control group –  $7.2 \pm 1.6$  and  $8.6 \pm 1.2$  ( $p_1-p_2 > 0.05$ ).

**Conclusions.** Comprehensive prophylaxis of non-pregnancy in multiple pregnancies, combining the use of a traumatic cardiac cervix with the help of unloading obstetric pussies with progesterone preparations, allows prolonging pregnancy, preventing the development of prematurity, contributes to the improvement of perinatal indicators.

## Keywords

multiple pregnancy; miscarriage; unload obstetrical pessary

<sup>1</sup> Sumy State University, Sumy, Ukraine

<sup>2</sup> Ternopil State Medical University, Ternopil, Ukraine

<sup>3</sup> National Medical Academy of Postgraduate Education, Kyiv, Ukraine

\*Corresponding author: [nikitina1med@gmail.com](mailto:nikitina1med@gmail.com)

## Problem statement and analysis of the recent research

Non-pregnancy is the most common complication of gestational process in women with multiple pregnancies. Prematurity frequency is 54.3%, if compared with 12% at single-pregnancy. Lost pregnancies make up almost 17% of all desirable, herewith 75-80% of miscarriages occurring on the early stages, and, unfortunately, there is no tendency to decreasing these indicators [1, 2, 3]. In this regard, the maximum pro-

longation of multiple pregnancies is an important condition for reducing perinatal morbidity and mortality in this group of high-risk patients [3, 5].

A whole chain of pathogenetic factors takes part in realizing miscarriage in multiple pregnancies. They include placental dysfunction, istmicocervical insufficiency, infectious-inflammatory process, immune reactions and congenital or acquired thrombophilia, extra genital diseases, neuroendocrine disorders, most of which are accompanied by gestagens in-

sufficiency starting at the stage of pre-gravida preparation [5, 8, 9]. No effective way is proved to prevent premature birth during multiple pregnancies. Overextension of the lower segment of the uterus and excessive pressure on the cervix often lead to the development of istmicocervical insufficiency (ICI) [7, 9].

It's demonstrated in a series of randomized trials that progesterone is an effective means of preventing premature birth in pregnant women in high risk group (premature birth history or shortening of the cervix), the use of progesterone in the prenatal period leads to a reduction in the preterm pregnancy rate by 35%.

British experts conducted a research from the evaluation the value of progesterone in preventing of premature births with double (STOPPIT – Study of Progesterone for Preventing the Preterm Birth in Twins). It was concluded that the use of progesterone in a double does not reduce the frequency of premature birth or fetal death before 34 weeks of gestation [6]. Perhaps this is connected with insufficient dosage of progesterone drugs. According to recent scientific data, progesterone suppresses the expression of genes responsible for the contractile activity of myometrium, is an antagonist of prostaglandin F2 $\alpha$ . It inhibits the activity of prostaglandins by inhibition of their precursor – arachidonic acid. In recent years, it's disclosed the basic (first of all, immune) mechanisms of the implementation of progesterone at prophylaxis due to the fetus. The main mechanism that contributes to the preservation of pregnancy is associated with the immunological features of pregnancy – a progesterone-induced blocking factor (PIBF). It is produced in the presence of a sufficient amount of progesterone and prevents the rejection of a fetal egg, which contains alien maternal antigens in the parent, and is perceived as an allograft [9, 10].

It was noted that the tocolytic property is inherent to the natural metabolites of progesterone (5b-pregnanonone, 5b-pregnandiol and 5b-pregndion), which is formed by the interaction of progesterone with the 5b-reductase enzyme and initiate a strong tocolytic effect, which is possible only with the identity of natural progesterone, and therefore synthetic analogues of progesterone do not have such properties [6, 7].

The drug of Lutein is a modern, innovative form of natural micronized progesterone for sublingual and vaginal use, which is identical to endogenous. It creates maximum concentration in plasma of blood and target organs, does not undergo primary metabolism in the liver, which allows to achieve maximum concentration in the blood at low dosages and to choose the most convenient way of input. Sublingual form is the unique form of natural micronized progesterone in the world; its advantages are rapid removal of clinical symptoms and regression of ultrasound markers of the threat of abortion, shorter period of staying in a hospital [7, 8]. The optimal combination of different forms of micronized progesterone is a combination of sublingual and vaginal form.

According to the recommendations of the European Society of Obstetricians-Gynecologists in 2011, it's recommended

the appointment of a vaginal form of progesterone in the case of high risk of premature birth from the beginning of the 2nd and during the third trimester of pregnancy. Society for Maternal-Fetal Medicine in 2012 recommends the use of vaginal progesterone since the installation of diagnosis of premature birth (even asymptomatic women for uterine cervical length  $\leq 20$  mm) and before the 36th week of pregnancy. It was found that at the background of using micronized progesterone, the risk of premature birth in the term to 34 weeks of pregnancy is reduced by 42%, in addition, the incidence and mortality rate of newborns, the development of respiratory distress syndrome (RDS) are significantly reduced to 52-61%, and the need for artificial ventilation of the lungs is reduced too (R. Romero et al., 2012) [8].

However, despite the proven high effectiveness of progesterone therapy of danger of premature birth, the issue of prescribing micronized progesterone drugs, the most optimal form of drug administration and the duration of treatment remains discursive.

**The objective of the research:** to sum up the effectiveness of the using the unloading obstetric pessaries in combination with micronized progesterone in women with multifetal pregnancy and high risk of non-compliance.

## 1. Materials and methods

The research was conducted on the basis of the Sumy Regional Clinical Perinatal Center during 2012-2016. We analyzed 120 cases of multiple pregnancies with signs of miscarriage in terms of 16 - 28 weeks. The first group of the examined patients consisted of 40 double-pregnant women with signs of non-pregnancy, which in the scheme of treatment-prophylactic measures were suggested the use of unloading obstetric pessary in combination with continuous therapy by natural micronized progesterone for the period of 36 weeks of gestation. The second group consisted of 40 pregnant women with twins, who had a septum on the cervix in connection with istmicocervical insufficiency, and short-term courses of progesterone therapy. The control group consisted of 40 twin pregnancies in the period of 16 - 28 weeks of gestation which were being treated for the risk of miscarriage in accordance with the current clinical protocols. In addition to clinical examination methods and generally accepted laboratory studies, transvaginal cervicometry was performed to assess the threat of pregnancy interruption (PI), as well as an assessment of the state of the cervix according to Stemberg, where the score of 5 and higher was indicative for the prevention and treatment of the threat of abortion.

Transvaginal cervicometry was performed with the help of the modern ultrasound apparatus "MEDISON" using transvaginal sensor of 6.5 MHz. At later dates of convective sensors 3.5 and 5 MHz in two-dimensional echo modes in accordance with terms of 10 - 13 weeks, it determined the viability, number of fetus, and the number of choriones, the thickness of the collar space, the birth defects, and the exact term of gestation. In the later period within 18-22 and 28 - 34 weeks of

pregnancy, – ultrasound photometry was performed; placenta researches included measurement of its thickness and evaluation of the degree of maturity by P.Grannum et al. (1979).

The main criteria for the threat of abortion were a shortening of the cervix to 2.0 cm or more, the opening of the cervical canal at 0.9 cm and above, and the ratio of the length of the cervix to its diameter at the level of internal cavity – 1.16 cm.

Pessary was carried up to a pregnant woman within 18 - 28 weeks in the outpatient conditions and in a hospital. Regular bacteriological examination of vaginal smears, transvaginal cervicometry and the control of the location of pessary every 3 to 4 weeks were performed on women after the introduction of pessary. The mechanism of action of the pessary is to reduce the burden of the intrauterine pressure of the fetal egg, the closure of the cervix through the walls of the central opening of the pessary, the formation of a shortened and partly open cervix and the reduction of pressure on it due to physiological sacralization of the cervix and a partial transfer of intrauterine pressure to the anterior wall of the uterus, the preservation of the mucous membrane. Indications for the introduction of obstetric discharge pessaries were: the risk of non-pregnancy associated with progressive changes in the cervix in patients with multiple pregnancy, including those after using ART, as well as patients with multiple pregnancies, which had a history miscarriage at a later date, premature birth, and the usual miscarriage of pregnancy. Contraindications to the introducing the obstetric pessary were also taken into account: recurrent bleeding from the genital tract in the 2nd-3rd trimester of pregnancy, expressed by the ICI with prolapse of the productive bladder and violation of its integrity. In inflammatory diseases of the vagina, cervix, external genitalia, a preliminary sanitation of the infection was carried out with subsequent bacteriological control.

In the planned order, obstetric pessary was withdrawn in 37 weeks of pregnancy or with the onset of labor. Before the introduction of the pessary, the sanitation of the genital tract was carried out with an antiseptic agent, taking into account the peculiarities of the micro biocenosis of the vagina. Along with the introduction of unloading obstetric pessaries women of group 1 were assigned natural micronized progesterone of Lutein in the form of sublingual and vaginal form. Dosage formulation and method of use: in women of the 1st group with premature birth - micronized progesterone 200 mg vaginal from 16 - 20 to 34 - 37 weeks; with a short cervix (length in the second trimester shorter than 15 mm) – lutein, micronized progesterone vaginal 200 mg from 16 - 20 to 34 - 37 weeks of gestation. Sublingual tablets were given 1 for 100 mg (2 tablets) 3 times a day, at the risk of miscarriage, premature birth, as a pregradar preparation. In addition, a pregnant with twins after IVF during 77 days after the transferring the embryos was prescribed a sublingual form of Lutein for 100 mg 3-4 times a day. The presence of sublingual and vaginal forms of micronized progesterone allows to go from one form to another if needed and simultaneously combine the use of both forms for the rapid saturation of the body with pregnant

progesterone in conditions of progesterone deficiency to eliminate the symptoms of the threat of abortion. At the time of being in a hospital, in the presence of signs of the threat of abortion, a tocolytic therapy with nifedipine was prescribed for 48 hours.

Pregnant of group 2 was assigned tocolytic therapy with nifedipine for 48 hours during the period of surgical cardiac surgery, during the staying in a hospital, synthetic progesterone (dydrogesterone) preparation was included in short-term courses under the control of the level of progesterone in the blood of the pregnant woman. The evaluation of the effectiveness of the proposed prophylactic treatment scheme was based on clinical and laboratory monitoring of pregnancy and fetus, as well as a comparative analysis of pregnancy outcomes in the women surveyed.

Statistical processing of the material was carried out using the methods of variation and paired statistics, and also using the method of difference using Student's t-criterion [4]. The obtained results were considered reliable if the coefficient of reliability  $p$ , which was found on the Student's table, was less than 0.05.

## 2. Results of the research and their discussion

The average age of pregnant women probably did not differ. Thus, in the examined group I, it was  $28.5 \pm 1.5$  years, in the group II –  $29.0 \pm 1.4$ , in the control group –  $27.5 \pm 1.6$  ( $p > 0.05$ ). By parity, half of the women in group I were pre-pregnant, the rest of the women had repeated pregnancies, all pregnant women had obsessive obstetric history (medical abortions, involuntary miscarriage, dead pregnancy), of which 11 women had a previous pregnancy with normal childbirth, 9 had in history spontaneous abandonment and abortion. In 17 (42.5%) patients of the group II, this pregnancy was the first, the remaining 23 women had repeated pregnancies, 18 (45%) patients had involuntary miscarriages and abortions in history. Extragenital pathology was not surveyed.

The main criteria for the threat of abortion were a shortening of the cervix to 2.0 cm or more, the opening of the cervical canal at 0.9 cm and above, and the ratio of the length of the cervix to its diameter at the level of internal cavity – 1.16 cm.

During the transvaginal cervicometry, it was found that the pace of cervical shortening in multiple pregnancy significantly exceeded those with unipolar. Under the threat of premature birth, the length of the cervix was  $19 \pm 2.3$  mm, with changes in the cervix not only being shortened, but also by the V- or U-like opening of the internal lobe and cervical canal. In patients with double cervical length  $< 19$  mm is a risk criterion for “early” preterm labor. These pregnant women were given the prophylactic therapy of the threat of preterm labor.

By 22-24 weeks, multifetal pregnancies indicated lower cervical length indices than those with single pregnancy:  $27.5 \pm 4.5$  mm in patients of group II against  $32.2 \pm 4.9$  mm in group I and  $28.7 \pm 3.7$  mm – in the control group. The dynamics of cervical shortening was significantly slower in

**Table 1.** Length of cervix in ultrasound examination

Term of pregnancy, weeks	Control group, mm	Group II, length of the cervix, mm	Group I, length of the cervix, mm
Less than 15	35.4±5.6	32.2±5.43	35.2±4.3
16-18	34.3±4.3	31.02±5.12	34.0±3.9
19-21	31.3±3.8	30.9±5.5	33.3±4.2
22-24	28.7±3.7	27.5±4.5	32.2±4.9
25-27	26.7±3.6	27.2±3.5	31.2±4.5
28-30	25.1±2.5	26.15±3.9	29.2±4.1
31-33	23.8±3.2	25.3±4.2	27.2±4.0
34-36	21.4±3.1	21.6±4.4	23.8±3.1

group I patients, who had been assigned an unloading obstetric pessary and assigned a natural micronized progesterone.

In the introduction of obstetric pessary there was no complication in any of the pregnant women in the first group, even with prolonged use of pessary for 20 weeks, no cases of trophic complications of the vagina were noted. In 6 (12.5%) pregnant women it was necessary to treat vaginal candidiasis to remove pessary. Tocolytic therapy according to the Order of the Ministry of Health # 624 was performed in 13 (32.5%) women in the presence of complaints of pain in the abdomen, both before and after the introduction of pessary. The analysis of clinical results of the application of the complex method of treatment and prevention of non-pregnancy in pregnant women with multiple pregnancies using unloading obstetric pessary in combination with natural micronized progesterone is represented in Table 2.

Thus, the reduction of clinical symptoms of AR (abortion risk) in group I was already observed at  $1.5 \pm 1.0$  days, in the control group –  $2.0 \pm 1.2$ , in the group II –  $3.0 \pm 2.0$  days, regression of ultrasound markers of AR (normalization of the thickness of the myometrium, narrowing of the lumen of the cervical canal and slowing down the dynamics of the cervix shortening) were noted for  $3.2 \pm 0.5$  days in group I, in the control group – by  $3.5 \pm 1.2$  days, and by  $4.0 \pm 1.0$  days in pregnant women in group II.

In the group I, overweight occurred in 34 (85%) cases, in the group II – in 29 (72.5%) cases, and in the control group – 25 (62.5%) cases. The course of childbirth was complicated by premature rupture of the membranes (PRM) in 7 (17.5%) patients in Group I, 10 (25.0%) women in the group II and 13 (32.5%) in the control group, the anhydrous interval did not exceed  $8.4 \pm 1.5$  hours and  $12.4 \pm 2.3$  hours accordingly ( $p < 0.05$ ). The average duration of childbirth was  $10.4 \pm 2.3$  in the group I,  $8.6 \pm 1.5$  hours in the second group and  $9.5 \pm 2.6$  hours in the control group. Blood loss in childbirth through natural delivery lines was on average in women of the group I –  $290 \pm 25$  ml,  $315 \pm 27$  ml in the second group and  $320 \pm 37$  ml in the control group. There was no pathological blood loss during childbirth due to natural birth lines in the groups under investigation.

Childbirth by Caesarean section was performed in 7 (17.5%) pregnant of the group I, in 9 (22.5%) patients of the II group and in 11 (27.5%) pregnant of the control groups. In the control group, premature birth occurred in 15 (37.5%) pregnant women, perinatal losses were 2.5% (one newborn). In pregnant women of the 2nd group, which was the subject of surgical treatment of the ICI, chorioamnionitis developed in one case; therefore, antibiotic therapy and circular suture were prescribed, this pregnancy occurred within a period of 28 weeks, there was a perinatal loss of one newborn, which was 2.5%.

The duration of stay in the hospital was  $12 \pm 1.2$  days in women of group I;  $21 \pm 1.6$  days in the group II and  $18 \pm 1.3$  in the control group ( $p < 0.05$ ).

The following results were obtained in studying the state of neonatal adaptation of newborns. The average weight of newborns of the group I was  $3245 \pm 280$  g, in the group II  $2865 \pm 365$  g, in the control group  $2975 \pm 325$  g ( $p > 0.05$ ). Evaluation of the state of newborns by using the Apgar scale at the 1-st and 5-th minutes was, accordingly, in the newborns of the group I:  $7.5 \pm 1.4$  and  $8.4 \pm 1.3$  points, in the second group –  $7.3 \pm 1.6$  and  $8.2 \pm 1.1$  points, in the control group –  $7.2 \pm 1.6$  and  $8.6 \pm 1.2$  ( $p_1-p_2 > 0.05$ ).

### 3. Conclusions

Thus, according to the results of the study, the following conclusions can be drawn:

1. The use of unloading obstetric pessary is an effective method of prevention and treatment of pregnancy loss in pregnant women with multifetal pregnancies, reducing the frequency of late abortion and preterm childbirth, perinatal loss due to total exposure, leading to closure and sacralization of the cervix, redistribution of the pressure of the fetal egg, better formation of the truncated and partially exposed cervix.
2. The method of usage unloading obstetric pessary is pathogenically reasonable in pregnant women with multiple pregnancies and allows prolonging pregnancy to terminate in 85% of women in the study group, reducing the medication burden on pregnant women and fetus.
3. The combined use of noninvasive cardiology and micronized progesterone reduces the risk of premature birth more than twice. The use of natural micronized progesterone promotes the rapid elimination of clinical symptoms and regression of ultrasound markers of the threat of abortion, shortens the term of being in hospital, and promotes 50% reduction in the number of complications compared with other gestagens.
4. In the application of non-invasive cerclage, it is more appropriate to prescribe the sublingual form of micronized progesterone, since the use of pessaries may violate the absorption of the vaginal form of progesterone.



Table 2

Survey group	Number of women	Reducing clinical symptoms of AR, day	Regression US-markers of AR, day	PRM, number of cases,%	Duration of stay in hospital, days
Control group	40	2.0±1.2*	3.5±1.2*	13 (32.5%)*	18±1.3*
Group II	40	3.0±2.0**	4.0±1.0**	10 (25.0%)**	21±1.6**
Group I	40	1.5±1.0	3.2±0.5	7 (17.5 %)	12±1.2

Note: \*- the index of reliability between groups.

## References

- [1] Baranov YY, Tokova ZZ, Tadevosian AA. Perinatal outcomes in multiple births. *Akusherstvo i hinekologiya*. 2012; 1: 98-102.
- [2] Vdovychenko YuP. Multiple pregnancy: A manual. Part II (for the enclave). Kyiv: 2011: 360.
- [3] Krasnopolskiy VY, Novykova SV, Kapustyna MV, Tytchenko LY, Aksenov AN, Zharova AA. Modern problems of multiple pregnancies. *Rossiyskiy vestnik akushera-ginekologa*. 2009; 2: 79-81.
- [4] Botting BJ, MacDonald-Davies I, MacFarland AJ. Recent trends in the incidence of multiple birth and associated mortality. *Arch. Dis. Child*. 2011; 62: 941-948. DOI: <https://doi.org/10.1136/adc.62.9.941>
- [5] Almonte L, Davis M, Ward C, Brown D, Craparo F. Spontaneous and non-spontaneous twins: a comparasion study of preterm labor, preterm premature rupture of membranes, gestational age at delivery, maternal age, and lenth of hospital stay. *Twin Research and Human Genetics*. 2012; 15: 2: 170.
- [6] Hassan SS, Romero R. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, doubleblind, placebocontrolled trial. *Vidyadhari et al. Ultrasound in Obstetrics & Gynecology*. 2011; 1: 18-31. DOI: <https://doi.org/10.1002/uog.9017> [PMid:21472815 PMCid:PMC3482512]
- [7] Management of preterm labor. Practice Bulletin No. 127. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012; 119: 1308-13. DOI: <https://doi.org/10.1097/AOG.0b013e31825af2f0> [PMid:22617615]
- [8] 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*. 2012; 2 (124): 1-19. DOI: <https://doi.org/10.1016/j.ajog.2011.12.003>
- [9] Salazar EL, Calzada L The role of progesterone in endometrial estradiol and progesterone-receptor synthesis in women with menstrual disorders and habitual abortion. *Gynecol. Endocrinol*. 2007; 23 (4): 222-225. DOI: <https://doi.org/10.1080/09513590701254030> [PMid:17505942]
- [10] Use of progesterone to reduce preterm birth/American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2008; 112: 963-965. [PMid:18827143]
- [11] Lapach SN, Chubenko AV, Babych PN. Statistical methods in biomedical research using Exel. Kyiv: Moryon: 2000; 320.

Received: 24 Oct 2017

Revised: 4 Dec 2017

Accepted: 26 Dec 2017