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ORIGINAL ARTICLE



# Effectiveness of dydrogesterone, 17-OH progesterone and micronized progesterone in prevention of preterm birth in women with a short cervix

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**ABSTRACT**

**Objective:** To compare the efficacy of dydrogesterone, 17-OH progesterone (17OHP) and oral or vaginal micronized progesterone with cerclage for the prevention of preterm birth in women with a short cervix.

**Methods:** The study included 95 women with singleton gestation and cervical length (CL) $\leq$25 mm. Among these, 35 women were asymptomatic at 15–24 weeks and 60 had symptoms of threatened late miscarriage (LM) or preterm delivery (PD) at 15–32 weeks. Patients were randomized to receive dydrogesterone, 17OHP or oral/vaginal micronized progesterone; after one week of therapy 15 women underwent cerclage.

**Results:** Efficacy of vaginal progesterone (VP) for the prevention of preterm birth reached 94.1%. In asymptomatic women pregnancy outcomes were comparable to cerclage. In women with threatened LM/PD, combination therapy with VP, indomethacin and treatment of bacterial vaginosis (BV) with the subsequent use VP until 36 weeks together with CL monitoring significantly decreased the rate of preterm birth (RR 0.01; 0.0001–0.24) and low birth weight (LBW) (RR 0.04; 0.01–0.96). CL increase during the first week of treatment with a subsequent plateau phase indicated treatment efficacy. Dydrogesterone, 17OHP, and micronized oral progesterone (OP) were associated with PD in 91.7% of women.

**Conclusions:** Combination management strategy including VP significantly benefits pregnancy outcomes in women with a short cervix compared with cerclage. Dydrogesterone, 17OHP, and OP were not found to be efficacious.

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Vaginal progesterone; indomethacin; bacterial vaginosis; preterm birth; short cervix

Preterm birth remains one of a major medical issue worldwide and its significance lies not only in the loss of a desired pregnancy, but also the birth of a premature baby. Prematurity is considered to be the main factor of perinatal morbidity and mortality. Neonatal morbidity subsequently leads to adverse health outcomes, thereby increasing the risk of serious physical and psychological impairment, and high economic costs [1].

Etiology of preterm birth is attributed to complex pathological processes. However, the majority of preterm deliveries occur in women without any evident risk factors [2]. Currently there is no distinct scoring system to predict preterm birth. In addition, the management of ongoing LM/PD is not sufficiently effective. Beta-mimetics, calcium-channel blockers, inhibitors of prostaglandin synthesis, oxytocin receptor antagonists administered to decrease the probability of delivery within 2–7 days, however, do not affect PD rate [3–5]. Preventative long-term administration of any tocolytic drugs does not affect the rate of PD [6,7].

The main symptoms of threatened LM/PD are regular uterine contractions and cervical shortening. The risk of PD in women with uterine activity, without cervical ripening is less than 2%. At the same time, pregnancies in which both the symptoms are present result in PD in most cases [8]. Asymptomatic short cervix is defined as a transvaginal (TV) sonographic CL $\leq$25 mm in mid-trimester of pregnancy. This condition is considered to be a highly unfavorable prognostic factor for adverse pregnancy outcomes, and has also been recognized as one of the strongest and consistent predictors of PD [8–10]. The risk of PD in women with singleton gestation and CL $\leq$25 mm is 20%, and with $\leq$15 mm – 50%, whereas 96% of women with CL $>$25 mm completed their pregnancies [11,12].

The cervix is composed of smooth muscle fibers, fibroblasts, epithelial cells, and blood vessels,

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surrounded by extracellular matrix of collagen, elastin, and proteoglycans. Cervical ripening is caused by complex biochemical processes of collagen restructuring and "loosening" of extracellular matrix, and does not correlate with uterine contractility [13]. Mechanisms of early cervical ripening remain unclear [12]. However, progesterone insufficiency is considered to be one of the main contributors to the process [14–16] that also participates in the triggering of uterine contractility. As the main hormone of pregnancy, progesterone reduces myometrial sensitivity to oxytocin, blocks adrenergic receptors and prostaglandin synthesis [16,17], and stimulates lymphocyte-associated synthesis of progesterone-induced blocking factor. Collectively, these mechanisms facilitate uterine quiescence during pregnancy, control cervical functions, and immune tolerance [18].

A systematic review [19] of 36 randomized controlled clinical trials including 8523 women with a short cervix and 12,515 newborns has shown that administration of progesterone (VP, 17OHP) between 20–36 weeks of pregnancy significantly reduces the PD rate (RR 0.64), perinatal mortality, neonatal morbidity and the risk of LBW (RR 0.55, 0.74, and 0.92, respectively) versus placebo. The efficacy of VP therapy was later reaffirmed by a meta-analysis by Romero, including 974 women. PD risk rate accounted for 18.1% compared with 27.5% in placebo group ($p = .0005$) [20]. Moreover, VP and OP have been found to be effective for threatened PD [21]. Considering the *in vitro* data, VP not only independently inhibits myometrium contractility but also enhances the tocolytic activity of indomethacin and nifedipin ($p < .05$) [22]. The efficacy of long-term VP use after successful tocolysis for PD prevention remains controversial [23,24]. At the same time, the effects of dydrogesterone and 17OHP on delayed delivery are not well-studied too. It was found that 17OHP did not prevent cervical insufficiency in women with a short cervix and did not reduce uterine contractility [25,26], thereby increasing the risk of LM/PD and perinatal mortality rates [27,28]. According to a randomized placebo-controlled trial published in 2016, dydrogesterone did not affect uterine contractility, the latency length, and pregnancy outcomes in women with threatened PD [29].

A substantial proportion (25–40%) of preterm births is attributed to intrauterine infection as a result of BV [10,30]. However, despite a well-characterized association between BV and PD, no differences in the vaginal microbiome in women with term and PD have been found [31]. Some studies revealed that antibacterial therapy for BV did not prevent PD [30]. Nevertheless, the risk of preterm birth is associated not only with vaginal microbiome composition but is also related to microbial activity and exposure time of the cervix and fetal membranes. Recent studies have demonstrated a high value of biochemical microbial metabolism markers in the prediction of PD [32,33]. Other studies have shown that treatment of BV at the first weeks of pregnancy significantly reduces the risk of LM and PD (by 80% and 40%, respectively) [34]. Upper colonization of the cervix and fetal membranes with vaginal microflora causes inflammatory response. Leukocyte infiltration, activation of lipopolysaccharides, peptidoglycans, proinflammatory cytokines, and chemokines trigger the cascade of matrix metalloproteinase and prostaglandin synthesis [15,35,36]. Eventually, these changes can lead to cervical ripening, preterm premature rupture of membranes (PPROM), uterine contractility, and preterm birth [31,35].

The aim of our open label study was to evaluate the efficacy of complex strategy, involving the use of progesterone, tocolytics, and BV treatment, for the prevention of preterm birth in women with singleton pregnancies

## Phase 1: Preliminary randomized clinical study to evaluate the efficacy of dydrogesterone, 17OHP, OP, and VP for the prevention of preterm birth in women with a short cervix

### *Methods*

The study was conducted in the Scientific Centre of Obstetrics, Gynecology and Perinatology of Moscow, Russia (2005–2007). 646 women underwent TV sonography at 15–24 weeks, and 52 women with a CL $\leq$25 mm were included in the study on an intent-to-treat basis. Among these, 25 patients had asymptomatic short cervix and 27 had symptoms of threatened LM/PD (lower abdominal pain and three to five uterine contractions per hour). Mean age of the patients was $29 \pm 4.76$ years, and parity range was $2.1 \pm 0.8$. Women with severe concomitant conditions, history of cervical surgery, congenital fetal, and uterine anomalies were excluded.

The women were randomized to four groups to receive the following therapy: dydrogesterone 30 mg/day orally ($n = 15$), 17OHP 250 mg i.m. QW ($n = 10$), OP 400 mg/day ($n = 12$), and VP (capsules) 400 mg/day ($n = 15$) (Table 1). There were no significant differences in medical history between the groups ($p > .05$).

A short cervix has always been associated with vaginal discharge. BV was diagnosed based on Amsel criteria after ruling out the presence of sexually transmitted diseases (STDs). The additional BV treatment

**Table 1.** CL and uterine contractility after 1 week of progestogenes treatment and pregnancy outcomes in subgroups a, B, C and cerclage ($n = 52$).

| | CL (mm) | | Uterine contractility | | | |
|---|---|---|---|---|---|---|
| Women with CL≤ 25 mm at 14–25 weeks | At baseline | Follow-up after 1 week of treatment | At baseline | After 1 week of treatment | Subgroup | LM/PD (weeks) |
| Dydrogesterone group ($n = 15$) | | | | | | |
| Seven asymptomatic women | 25 | 0 | – | – | A | 34 |
| | 25 | 0 | – | – | A | 33 |
| | 24 | 0 | – | – | A | 31 |
| | 23 | 0 | – | – | Cerclage | – |
| | 22 | 0 | – | – | Cerclage | – |
| | 22 | 0 | – | – | Cerclage | – |
| | 20 | 0 | – | – | Cerclage | 35 |
| Eight women with threatened LM/PD | 24 | −13 | + | + | B | 19 |
| | 15 | −8 | + | + | B | 20 |
| | 25 | −4 | + | + | Cerclage | – |
| | 20 | −6 | + | + | Cerclage | 28 |
| | 25 | −5 | + | + | C | – |
| | 25 | −9 | + | + | C | – |
| | 25 | −3 | + | + | C | – |
| | 22 | −4 | + | + | C | – |
| 17P group ($n = 10$) | | | | | | |
| Six asymptomatic women | 25 | 0 | – | – | A | – |
| | 24 | 0 | – | – | A | 35 |
| | 25 | 0 | – | – | Cerclage | 35 |
| | 25 | 0 | – | – | Cerclage | – |
| | 24 | 0 | – | – | Cerclage | – |
| | 22 | 0 | – | – | Cerclage | – |
| Four women with threatened LM/PD | 20 | −7 | + | + | B | 22 |
| | 25 | −13 | + | + | B | 24 |
| | 25 | −2 | + | + | C | – |
| | 20 | −5 | + | + | C | – |
| OP group ($n = 12$) | | | | | | |
| Five asymptomatic women | 25 | 0 | – | – | A | 34 |
| | 25 | 0 | – | – | Cerclage | – |
| | 25 | 0 | – | – | Cerclage | – |
| | 24 | 0 | – | – | Cerclage | – |
| | 24 | 0 | – | – | Cerclage | – |
| Seven women with threatened LM/PD | 25 | −3 | + | + | B | 28 |
| | 22 | −8 | + | + | B | 25 |
| | 18 | −6 | + | + | Cerclage | 36 |
| | 25 | −3 | + | + | C | – |
| | 25 | −7 | + | + | C | – |
| | 25 | −5 | + | + | C | – |
| | 20 | −5 | + | + | C | 24 |
| VP group ($n = 15$) | | | | | | |
| Seven asymptomatic women | 25 | +5 | – | – | A | – |
| | 25 | +4 | – | – | A | – |
| | 25 | +2 | – | – | A | – |
| | 23 | +3 | – | – | A | – |
| | 20 | +3 | – | – | A | – |
| | 20 | +6 | – | – | A | – |
| | 20 | +12 | – | – | A | – |
| Eight women with threatened LM/PD | 25 | 0 | + | + | C | – |
| | 24 | 0 | + | + | C | – |
| | 22 | −5 | + | + | C | 24 |
| | 22 | −7 | + | + | C | 22 |
| | 20 | −10 | + | + | C | 21 |
| | 20 | 0 | + | + | C | – |
| | 18 | 0 | + | + | C | – |
| | 15 | 0 | + | + | C | – |

included a 3-day course of 100 mg clindamycin, followed by a 7-day course of probiotics intravaginally. In the VP group, these vaginal agents were applied at least 1 h after VP administration, to ensure its complete vaginal absorption [37].

After 7 days of treatment, women were randomly assigned to the following four subgroups:

- Cerclage ($n = 15$): 12 asymptomatic women and 3 women with threatened LM/PD who underwent

cerclage combined with hexoprenaline tocolysis i.v. for 2–5-days;
- A ($n = 13$): 13 asymptomatic women who continued on the same progesterone formulation;
- B ($n = 6$): women with threatened LM/PD who continued dydrogesterone, 17OHP or OP with hexoprenaline tocolysis i.v. for 2–5 days;
- C ($n = 18$): women with threatened LM/PD who were allocated to receive VP 600 mg/day (single dose 400 mg, then 200 mg 3 TID) with indomethacin tocolysis (100 mg BID per rectum on days 1–3, followed by 100 mg/day on days 4–7; total dose – 1000 mg). After the tocolysis had been completed, the patients continued to receive VP 400 mg/day followed by VP 200 mg/day until 36 weeks of gestation.

All patients were assessed for CL, uterine contractility, fetal heart rate, and side effects at weeks 1, 5, and 9 of therapy. We also recorded pregnancy outcomes in each subgroup.

### Statistical analysis

Statistical analysis was performed using Microsoft Office Excel 2003 software package and StatSoft Statistica 6.1.

## Results

### Dydrogesterone

After a week of dydrogesterone treatment, CL in seven asymptomatic women remained unchanged, whereas in eight women with threatened LM/PD the cervix further shortened by 3–13 ($-6.5 \pm 3.3$) mm and uterine contractility persisted. Subsequent dydrogesterone administration in both asymptomatic women (3/3) and with threatened LM/PD (2/2) did not prevent preterm birth, despite the use of tocolysis with beta-mimetics. After the replacement of dydrogesterone by VP 600 mg/day combined with indomethacin in four women with threatened LM/PD and progressive cervical shortening, uterine contractions disappeared and CL increased by 2–6 mm. Subsequent VP supplementations until 36 weeks maintained CL and resulted in term pregnancy.

### 17-OH progesterone (17OHP)

In six asymptomatic women after a week of 17OHP treatment, CL remained unchanged, whereas in four with threatened LM/PD it decreased by 2–13 ($-6.8 \pm 4.6$) mm while uterine contractility increased. Subsequent 17OHP administration was efficacious only in one out of four women. After the replacement of 17OHP by VP 600 mg/day combined with indomethacin in women with threatened LM/PD, uterine contractions stopped within a week and CL increased by 2–7 mm. As long as the dose of VP was maintained at 200 mg/day, CL remained stable and no symptoms of PD were observed.

### Oral progesterone (OP)

The dynamics of CL and uterine contractility were similar to those in the abovementioned groups. PD occurred in three out of three women who continued OP versus one out of four women who switched to the combination of VP with indomethacin, followed by maintenance VP.

### Vaginal progesterone (VP)

In asymptomatic women during the first week of VP treatment, CL consistently increased by 3–13 mm ($5.0 \pm 3.4$ mm) ($p < .05$) and remained stable during the maintenance VP therapy. All (7/7) pregnancies ended successfully. In women with threatened LM/PD, CL did not change or reduced by 5–10 mm, and uterine contractility was not inhibited. Five of these women were began to be administered an increased dose of VP, 600 mg/day, together with indomethacin and BV treatment. This led to the suppression of uterine contractility and an increase in CL by 3–9 mm after one week. CL remained unchanged after 1 and 2 months with no recurrence of threatened PD. However, other three women with threatened LM/PD, such as one woman in OP group, received the combination of VP/indomethacin without the BV treatment, which resulted in PPROM and preterm birth after 1–5 weeks.

### Cerclage

Incidence of preterm birth in women who further underwent cerclage occurred in 20%: with asymptomatic short cervix – 8.3% (1/12), with threatened LM/PD – 66.7% (2/3).

## Phase 2: Clinical study to evaluate the effectiveness of VP for the prevention of preterm birth in women with a short cervix

### Methods

After analyzing the data from the previous phase, we continued the clinical study to evaluate the efficacy of VP for the prevention of preterm birth in women with a short cervix. 550 pregnant women with singleton gestation underwent cervical examination with TV

sonography in the "KM-clinic", Moscow (2013–2016). After giving informed consent, 43 women with CL ≤25 mm were included in the study. The following exclusion criteria were used: severe maternal diseases, history of cervical surgery, congenital fetal, and uteri anomalies. 10 asymptomatic women with CL 15–25 mm at 15–24 weeks received VP 200 mg/day, in accordance with international guidelines [38]. 33 women with threatened LM/PD (23 – with CL 13–25 mm at 15–24 weeks and 10 – with CL 10–20 mm at 25–32 weeks) received tocolysis with VP/indomethacin, followed by a long-term VP administration. Additionally, BV treatment with clindamycin and probiotics was carried out.

The mean age of participants was 27 ± 4.85 years and parity range 2.0 ± 0.9. Medical, surgical, obstetric, psychosocial, and lifestyle history of the women did not differ between the groups ($p > .05$).

Follow-up assessments were conducted after 1, 5, and 9 weeks from the beginning of the therapy. In case of recurrent threatened LM/PD, VP dose was increased up to 600 mg/day during a week, with indomethacin tocolysis and subsequent cervical examination. After achieving a delay in delivery, VP dose was reduced to 200 mg/day for 1 week. Considering the previous study results, in case of recurrent or continued asymptomatic cervical shortening, VP dose was increased up to 400 mg/day for 1 week, followed by 200 mg/day and cervical examination a week later. Recurrent BV treatment was administered as appropriate.

### Results

*CL in asymptomatic women* after the first week of VP treatment in the 200 mg/day dose increased from 22.8 ± 3.2 mm to 26.4 ± 5.3 mm on average ($p = .0004$). In six women, CL increased by 2–12 mm and remained stable during the maintenance of 200 mg/day VP. In one pregnant woman who discontinued VP treatment for 2 weeks, CL reduced by 5 mm later, but returned to the previous value when VP therapy in the 400 mg/day dose was restarted for a week, followed by the maintenance dose of 200 mg/day afterwards.

Four women demonstrated no CL increase, and developed the signs of subsequent threatened LM/PD associated with CL shortening by 3–6 mm one month later. Increasing the VP dose up to 600 mg/day in combination with indomethacin contributed to the inhibition of uterine contractility and CL increase by 3–8 mm in a week. CL remained stable during the subsequent maintenance VP administration.

*In women with threatened LM/PD* after one week of indomethacin/VP treatment, CL increased by 3–11 mm (6.6 ± 2.3 mm) ($p < .05$). Symptoms such as lower abdominal pain and uterine contractions were not recorded in any of the patients. Women continued to receive VP 400 mg/day for another week with a subsequent dose reduction to 200 mg/day. 20 out of 33 women (60.6%) had stable CL and uncomplicated pregnancies. In nine women (27.3%), recurrently measured CL reduced by 4–9 mm (in eight women after one month and in one woman after two months), followed by symptoms of threatened LM/PD. After the recurrent indomethacin tocolysis, increasing the VP dose up to 600 mg/day for one week and BV treatment (in six patients with BV) resulted in suppressed uterine contractility and CL increase by 3–9 mm. In the other four (12.1%) women, including two who discontinued VP treatment at 26 and 29 weeks of gestation, cervical measurement showed asymptomatic shortening by 6–12 mm. After the administration of VP in the 400 mg/day dose for a week, CL increased by 5–9 mm and then remained stable during the VP maintenance phase. No deliveries occurred before 37 weeks of gestation.

## Summary results of phase 1 and 2

### *Pregnancy outcomes in women with a short cervix after dydrogesterone, 17OHP, OP, and VP treatment compared with cerclage*

A pooled analysis of pregnancy outcomes in women with a short cervix who were receiving different progesterone drugs compared with cerclage showed significant benefits of VP treatment for the prevention of perinatal complications in both asymptomatic women and those with threatened LM/PD. Beneficial pregnancy outcomes *in asymptomatic women* receiving VP were comparable with cerclage ($p > .05$) (Table 2). However, unlike cerclage, which was always associated with a post-surgery recurrence of BV, VP was not associated with side effects ($p = .001$). Conversely, in women from the dydrogesterone, 17OHP and OP groups, a significantly lower gestational age of delivery (23.3 ± 3.7 versus 34 ± 5.2 weeks) was observed. Latency to delivery (14.5 ± 3.9 versus 18.7 ± 2.8 weeks) and birth weight (2506.7 ± 479.2 versus 3320 ± 340 g) were also lower, The rate of LBW, preterm birth <37 or <32 weeks were significantly increased (RR 8.0, 21.0, and 8.0, respectively).

*In women with threatened LM/PD* who received progesterone therapy, CL continued to decrease and more active uterine contractility: dydrogesterone, 17OHP, OP – 100%, 19/19 (Table 1) and VP – 62,5%, 5/8 (Table 1, phase 2) was observed. Women (6/6)

**Table 2.** Pregnancy outcome measures in asymptomatic women with a short cervix after dydrogesterone, 17 P, OP, VP, and cerclage receiving ($n = 35$).

| | | Dydrogesterone, 17P, OP (6) | | | | VP (17) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pregnancy outcomes | Cerclage (12) | | $p^a$ | OR[a] (95%CI) | RR[a] (95%CI) | | $p^a$ | OR[a] (95%CI) | RR[a] (95%CI) |
| Gestational age of delivery (weeks) | 39.0 ± 0.5 | 34.2 ± 2.3 (Dydrogesterone 32.7 ± 1.5, 17P 36.5 ± 2.1, OP 34) | <.05 | | | 39.1 ± 0.4 | NS | | |
| Preterm birth <37w, *n* (%) | 1 (8.3) | 5 (83.3) | .0209 | 55 (2.83–1068.42) | 21.0 (1.48–67.56) | 0 (0) | NS | | |
| Preterm birth <34w, *n* (%) | 0 (0) | 4 (66.7) | .0720 | 17.31 (1.54–314.31) | 8.0 (1.13–56.79) | 0 (0) | NS | | |
| Preterm birth <28w, *n* (%) | 0 (0) | 0 (0) | NS | | | 0 (0) | NS | | |
| Latency to delivery (weeks) | 18.4 ± 5.6 | 14.5 ± 3.9 (Dydrogesterone 13 ± 2.0, 17P 17.5 ± 3.5, OP 16) | <.05 | | | 18.8 ± 7.5 | NS | | |
| Side effects, *n* (%) | 12 (100) | 0 (0) | .005 | 0.02 (0.01–0.35) | | 0 (0) | .001 | | |
| Birth weight (g) | 3320 ± 340 | 2506.7 ± 479.2 (Dydrogesterone 2200 ± 264.6. 17P 3050 ± 353.5. OP 2400) | <.05 | | | 3319 ± 440 | NS | | |
| Low birth weight (<2500 g) | 0 (0) | 4 (66.7) | .0720 | 17.31 (1.54–314.31) | 8.0 (1.13–56.79) | 0 (0) | NS | | |
| Perinatal mortality, *n* (%) | 0 (0) | 0 (0) | NS | | | 0 (0) | NS | | |

[a]Compared with Cerclage.

who continued dydrogesterone, 17OHP, or OP treatment regardless of the additional hexoprenaline tocolysis, experienced preterm birth in 1–5 weeks. Delayed delivery was achieved in only 33.3% women after the use of beta-mimetics tocolysis in combination with cerclage (Table 3). Higher VP dose combined with indomethacin proved to be the most effective in prolonging the pregnancy: 47 of 51 (92.2%) cases of threatened LM/PD, including nine recurrent, were prevented. The side effects rate of 5.9% with indomethacin (diarrhea) was significantly lower ($p = .0180$) than the 40.7% rate with beta-mimetics (headache, tachycardia, hands tremor, or constipation).

According to the recent studies, prostaglandins are essential for cervical ripening in preterm birth in contrast with term delivery [15]. A meta-analysis [5] of randomized clinical trials (3263 women) showed, compared to placebo, the probability of delivery being delayed by 48 h was higher with prostaglandin inhibitors (OR 5.39) than with β-mimetics, and side effects were significantly lower (OR 1.63, 0.40–6.85 and 22.68, 7.51–73.67, respectively).

BV treatment is a significant factor augmenting the efficacy of VP/indomethacin tocolysis. The therapy including VP, indomethacin, and BV treatment with prolonged VP in the dose of 200 mg/day until 36 weeks together with CL monitoring contributed to the risk reduction of PD <37 weeks compared with cerclage (RR 0.001; 0.0001–0.24), LBW (RR 0.04; 0.01–0.96), and increased gestational age at delivery, latency to delivery and birth weight. However, the results in all (4/4) women receiving VP/indomethacin therapy without BV treatment were found to be unsatisfactory: PPROM and PD were observed, and latency to delivery was only 1.5 ± 0.6 weeks.

### *Evaluation of the prognostic value of CL associated with the dydrogesterone, 17OHP, OP, and VP treatment in women with a short cervix*

According to the results obtained, increase in CL during the first week of treatment and its further stabilization is a strong and consistent predictor of successful pregnancy outcomes.

In our study, CL increase by 2–12 (6.6 ± 2.0) mm ($p < .001$) after the first week therapy was observed in 60 out of 68 women (88.2%) receiving VP. CL remained unchanged in 47 out of 60 (78.3%) women during the maintenance VP treatment. Initial CL increase and its further stabilization were associated with an uncomplicated pregnancy. The efficacy of treatment depended on the uterine activity before VP administration. In asymptomatic women, initial CL increase was always (13/13) associated with a beneficial outcome. Initial CL growth in women with threatened LM/PD was recurrent cervical shortening in 27.7% (13/47) and recurrent threatened LM/PD in nine of them (19.2%) ($p = .0113$).

**Table 3.** Pregnancy outcome measures in women with threatened LM/PD and a short cervix after dydrogesterone, 17 P, OP, VP, and cerclage receiving with hexoprenaline/indomethacine tocolysis ($n = 60$).

| Pregnancy outcomes | Cerclage + hexoprenaline (3) | Dydrogesterone, 17P, OP + hexoprenaline (6) | | | | [1]VP + indomethacine + BV treatment (47) [2]VP + indomethacine without BV treatment (4) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | $p^a$ | OR[a] (95%CI) | RR[a] (95%CI) | | $p^a$ | OR[a] (95%CI) | RR[a] (95%CI) |
| Gestational age of delivery (weeks) | 34 ± 5.2 | 23.3 ± 3.7 (Dydrogesterone 19.5 ± 0.7, 17P 23 ± 1.4, OP26.5 ± 2.12) | <.05 | | | [1]38.7 ± 0.3<br>[2]22.8 ± 1.5 | [1].042<br>[2].062 | | |
| Preterm birth <37w, *n* (%) | 2 (66.7) | 6 (100) | .5901 | 2.5 (0.10–62.61 | 1.5 (0.67–3.34) | [1]0 (0)<br>[2]4 (100) | [1].002<br>[2].69 | [1]0.001 (0.0001–0.24)<br>[2]1.5 (0.06–40.64) | [1]0.03 (0.01–0.26)<br>[2]1.13 (0.67–3.34) |
| Preterm birth <34w, *n* (%) | 0 (0) | 6 (100) | .2961 | 10 (0.40–250.43 | 3 (0.61–14.86) | [1]0 (0)<br>[2]4 (100) | [1]NS<br>[2].424 | [2]6.0<br>(0.22–162.54) | [2]2.25<br>(0.41–12.28) |
| Preterm birth <28w, *n* (%) | 0 (0) | 6 (100) | .2961 | 10 (0.40–250.43 | 3 (0.61–14.86) | [1]0 (0)<br>[2]4 (100) | [1]NS<br>[2].424 | [2]6.0<br>(0.22–162.54) | [2]2.25<br>(0.41–12.28) |
| Latency to delivery (weeks) | 13 ± 8.6 | 2.3 ± 1.3 (Dydrogesterone 1.5 ± 0.7. 17P 2 ± 0.5. OP 3.5 ± 2.1) | <.05 | | | [1]18.5 ± 6.8<br>[2]1.5 ± 06 | [1].062<br>[2]<.001 | | |
| Side effects, *n* (%) | 3 (100) | 3 (50%) | <.05 | | | 3 (5.9) | .004 | | |
| Birth weight (g) | 2800 ± 916 | 816 ± 475 (Dydrogesterone 400 ± 141.4, 17P650 ± 70.7. OP1400 ± 141.4) | <.05 | | | [1]3320 ± 341<br>[2]550 ± 129 | [1].046<br>[2]<.001 | | |
| Low birth weight (<2500 g) | 1 (33.3) | 6 (100) | .0720 | 10 (0.40–250.43) | 2.50 (0.49–12.89) | [1]0 (0)<br>[2]4 (100) | [1].246<br>[2].422 | [1]0.04 (0.01–0.96)<br>[2]6.0 (0.22–162.54) | [1]0.06 (0.01–0.79)<br>[2]2.25 (0.41–12.28) |
| Perinatal mortality, *n* (%) | 0 (0) | 4 (66.7) | .4743 | 4.0 (0.21–75.66) | 2.0 (0.37–10.92) | [1]0 (0)<br>[2]4 (100) | [1]NS<br>[2].413 | [2]6.0 (0.20–164.40) | [2]2.25 (0.50–12.78) |

[a]Compared with Cerclage.

The absence of CL increase during the first week of VP treatment in both asymptomatic women (4/4), those with threatened LM/PD (8/8), or CL shortening during the maintenance VP phase (12/12) was considered to be a prognostic factor of progressive threatened LM/PD.

The CL after the administration of dydrogesterone, 17OHP, and OP *in asymptomatic women* (18/18) initially remained stable. However, 83.3% (5/6) of those who continued receiving these drugs had PD. In all (6/6) women *with threatened LM/PD*, CL continued to decrease, and, regardless of additional tocolysis with beta-mimetics, uterine contractility could not be suppressed, which eventually led to PD too.

## *Summary result of the VP efficacy for the prevention of preterm birth in women with a short cervix*

### *VP 200 and 400 mg/day in asymptomatic women*

Ten asymptomatic women with a short cervix received 200 mg/day VP (Group I). In six (60%) of them, CL increased after a week of the treatment and remained stable until 36 weeks, while the patients continue to receive VP daily. In women without increasing CL during the first week of VP treatment, threatened LM/PD subsequently occurred. This observation was comparable to R. Romero's meta-analysis of the efficacy of VP in prevention of PD, in which a relative risk reduction of 0.51–0.79 was observed [20]. After the initial VP treatment in the 400 mg/day dose (in seven women of the VP group and in five women in Groups I and II with recurring cervical shortening, of whom three had discontinued VP therapy), CL increased ($p < .05$) during the first week of treatment and then remained stable; there were no symptoms of LM/PD during the maintenance VP phase in the 200 mg/day dose ($R = .468$, $p = .005$ compared with VP 200 mg/day).

### *VP 400 mg/day in women with threatened LM/PD*

In eight women in the VP group after a week of therapy, uterine contractility was not suppressed and CL continued to decrease. An increase in the VP dose up to 600 mg/day combined with indomethacin-delayed delivery increased CL by several mm.

### *VP 600 mg/day combined with indomethacin in women with threatened LM/PD*

Fifty-one women with threatened LM/PD and a short cervix (33 – in Group II (23 at 15–24 weeks, 10 at 25–32 weeks), eight – in the VP group, ten – in the

dydrogesterone, 17OHP and OP groups) received VP 600 mg/day and tocolysis with indomethacin for one week. In 47 women (92.2%) there was an inhibition of uterine contractility, which was followed by a CL increase by several mm. After the initial CL increase in women with threatened LM/PD, the risk of recurrent cervical shortening is 27.7% and recurrent threatened LM/PD occurred in 19.2% cases. After another round of the one-week tocolysis along with VP 600 mg/day and indomethacin (in women with threatened LM/PD) or VP 400 mg/day (in asymptomatic women with a short cervix), the condition of women returned to normal.

In four women with threatened LM/PD, VP/indomethacin therapy proved to be ineffective; cervical insufficiency progressed, leading to PPROM. The negative factor, in our opinion, was the absence of BV treatment, which was used in all remaining patients whose pregnancies resulted in term deliveries.

## Conclusions

This trial evaluated the efficacy of progesterone drugs in the prevention of preterm birth in women with a short cervix and provided compelling evidence of VP being much more effective compared with dydrogesterone, 17OHP and micronized OP, as well as cervical cerclage. Therapy with VP prevented preterm birth in 94.1% (64/68) women with a short cervix, which was more efficient than cerclage (73.3%, 11/15) ($p = .0126$ $\chi^2$) and other progesterone drugs (8.3%, 1/12, $p < .001$). Pregnancy outcome depended on dose of VP and uterine activity and correlated with CL ($R = .413$; $p = .017$). Further studies will contribute to the improvement of diagnostic and treatment strategies in women from risk groups, and will facilitate prevention of perinatal complications.

## Disclosure statement

No potential conflict of interest was reported by the author.

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