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Treatment of preterm labour in women with chronic infections

Svitlana Heryak and Nataliia Petrenko

Abstract
Objectives. To evaluate the efficacy of sublingual form of natural micronized progesterone and calcium channel blockers for treatment of threatened preterm labour in women that have had infections during pregnancy.
Methods: A retrospective analysis of case histories of pregnant women with preterm labour in gestational age 22-36 weeks was performed. Nature of complaints, history, structural changes of the cervix, concentration of pro- and anti-inflammatory cytokines were determined.
Results: Preterm labour occurred to employed women (79%), most of them (60%) are office workers with physical inactivity and computer. Preconditions for occurrence of preterm labour were complicated course of gestational process (36%), menstrual dysfunction (35%), infertility (24%), previous reproductive loss (22%), proliferative diseases of female reproductive organs (7%). 63% of patients had inflammatory diseases of respiratory tract, 33% – UTI, 20% – vaginal infections.
Using of natural micronized progesterone allowed to significantly decrease the levels of IL-2, IL-6, TNF-α, and increase the level of IL-4, IL-10 which was not significantly different from those in the control group. The level of pro-inflammatory cytokines also decreases and anti-inflammatory also increases in patients that received traditional therapy, but their values remained significantly different from those in control group and group I.
Conclusion: Chronic inflammation is launching an initial immune inflammatory response that is accompanied by insufficient secretion of endogenous progesterone and promotes the development of threatened preterm labour. Application 200 mg of sublingual form of micronized progesterone during 4 weeks provides rapid reduction of preterm labour symptoms which women with previous chronic infection had.

Keywords: preterm labour, inflammation, sublingual natural micronized progesterone

Introduction
Negative demographic situation in Ukraine in recent years occurred primarily because of low birth rates and low population growth. On the other hand, the deterioration of the socio-economic conditions, growth of "Millennium diseases" and chronic stress that accompany our life, have negative influence on reproductive function of women and create pregnancy loss [5].
Generally, reproductive losses are associated with interruption of pregnancy that is 22 - 25% of all ones. Each year, about 15 million babies are born prematurely, which is confirmed by European and American statistical data and compose from 12% to 46% of all perinatal pathology of infants [10]. Thus, prematurity takes first place in the structure of perinatal mortality, and this is 60-70% of early neonatal and 70-75% of infant mortality [6, 10].
According to the research conducted in recent years, there were distinguished a lot of criteria by which women belong to certain risk groups of preterm labour occurrence. In identification of different risk factors such as epidemiological, socio-demographic, constitutional factors, inflammatory, infectious and somatic diseases, obstetric history, complications of previous pregnancies, play an important role [9, 10].
Modern clinical approaches to resolving the problem of preterm labour consist in identification of risk factors, mechanisms of initiation of threatened preterm labour, characteristics of tocolysis and application of appropriate tactics [3, 7, 8].
However, despite significant advances of medical science in the field of tocolytic therapy of preterm labour, there still remains unresolved issue of predicting of the risk of preterm labour and application of effective methods of its prevention in pregnant women with high risk of its development, which is particularly important in modern obstetrics [4].
Therefore, despite the many scientific advances in the identification of the causes and methods of prevention of pregnancy loss, this issue is still important in the context of modern obstetrics.

The objectives of our research was evaluation of the efficacy of sublingual form of micronized progesterone for treatment and prevention of preterm labour in women with concomitant risk factors on the background of infectious component in history.

Material and Methods

Research was conducted in two stages. At the first stage of the research, 100 case histories of pregnant women with preterm labour in gestational age 22-36 weeks who were hospitalized in perinatal centre were analyzed. The complex evaluation of risk factors of preterm labour and effectiveness of its management was done. At the second stage of the research, for 27 pregnant women (group 1), with threatened preterm labour and infectious disease in history, natural micronized progesterone (Luteina) 100 mg was prescribed twice daily sublingually for 4 weeks [1]. For 30 pregnant women who before admission to the hospital were initiated traditional tocolytic therapy by calcium channel blockers were included in the comparison group (group 2). The control group consisted of 20 pregnant women with physiological pregnancy.

At admitting to the hospital there was evaluated the nature of complaints (regular cramping abdominal pain), history (past illnesses before and during pregnancy), obstetric examination (structural changes of the cervix), ultrasound (cervical size was compared to its indicators at the second screening). The level of anxiety of the pregnant was evaluated by Hamilton Anxiety Rating Scale (HAM-A). The concentration of pro-inflammatory (IL-2, IL-6, TNF-α) and anti-inflammatory (IL-4, IL-10) cytokines was determined at enzyme-linked immunosorbent assay analyzer (ELISA): STAT FAX 303 PLUS (USA) using a set of reagents and test systems for the quantitative determination thereof. Statistical analysis of the results was performed using statistical analysis software Microsoft Excel 7.0 and Statistica for Windows 6.0. Obtained results are presented as mean values and their standard error (M ± m). For the comparisons between the two groups there was used t-Student test. Null hypothesis is rejected at $p < 0.05$.

Results and Discussion

The analysis of case histories revealed that preterm labour at 22-26 weeks occurred in 15 (15%) women, at 26-34 weeks – in 75 (75%), at 34-36 weeks – in 10 (10%). The average age of patients was 21.3 ± 3.1 years. 60 (60%) of respondents had completed higher education, 15 (15%) – secondary education, 20 (20%) persons were university students, 5 (5%) – acquired secondary education. Most of pregnant women (60 (60%)) were office workers whose work was associated with using of computer, physical inactivity and / or uncontrolled working hours, in 19 (19%) women professional activity was accompanied by excessive physical activity.

Careful analysis of gynaecological, obstetric and physical history revealed that all pregnant women had some risk factors of preterm labour. It was found that pregnancy which was completed before the term in the quarter part (24 (24%) women) reached as a result of infertility treatment, among them in 10 (10%) women pregnancy became after hormone stimulation, in 8 (8%) – as a result of assisted reproductive technology, in 6 (6%) – after surgical restoration of tubal patency. Before pregnancy 77 (77%) patients had large amount of menstrual flow, 5 (5%) – irregular periods, 35 (35 %) – hypothalamus-pituitary-ovarian / adrenals imbalance, 14 (14%) – polycystic ovaries, 4 (4%) – follicular cysts, 2 (2%) – endometrial hyperplastic diseases (endometrial hyperplasia, polyps), 1 (1%) – uterine myoma. It should be noted that only 8 (8%) patients received the correction of hormonal imbalance more than 6 months before pregnancy.

Analysis of obstetric history revealed that 65 (65%) patients were primigravida, 35 (35%) – multigravida. Previous pregnancy was completed with term delivery in 23 (23%) women, miscarriages – in 5 (5%), preterm delivery – in 5 (5%), stillbirth – in 2 (2%). The threatened miscarriage in the first half of this pregnancy was diagnosed in 17 (17%) patients, in the second half – in 8 (8%).

16 (16%) pregnant had asymptomatic bacteriuria in the first trimester, 12 (12%) – exacerbation of chronic pyelonephritis during pregnancy, gestational pyelonephritis developed in 6 (6%), acute cystitis occurred to 4 (4%) cases. Just 22 (22%) pregnant women received antibacterial therapy for treatment of urinary tract infections.

Respiratory tract infections was diagnosed for 32 (32%) of the pregnant. Among them, 18 (18%) patients had acute respiratory viral infection, 8 (8%) – bronchitis, 4 (4%) – pneumonia, 2 (2%) – chronic sinusitis, exacerbation of chronic pharyngo-tonsilitis was noticed in 7 (7%) pregnant. Just 20 (20%) women received antibacterial therapy for treatment of respiratory tract infections.

Vaginal infections occurred to 20 (20%) pregnant, etiological factor has been identified as Tr. vaginalis in 6 (6%) patients, C. albicans – in 8 (8%), in other cases a mixed bacterial and fungal flora was detected.

Pregnant women were admitted to hospital with complaints of abdominal pain within 11.3 ± 1.2 hours after their appearance. 48 (48%) pregnant woman were previously hospitalized to the district hospital for a few hours where acute tocolysis by calcium channel blockers was performed and prophylaxis of fetal pneumopathy was started. Full course of prophylaxis of fetal pneumopathy (during 48 hours) was completed in 86 (86%) of pregnant women.

In the majority of cases (75%) preterm labour occurred at gestational age of 26-34 weeks within 57.3 ± 3.4 hours after hospitalization. As a result of this delivery 100 living children were born. The average weight of newborns was 1843.2 ± 162.3 g, Apgar scores at 1 minute was 7.3 ± 0.7 points, at 5 min – 7.9 ± 0.7 points.

Therefore, a comprehensive assessment of socio-biological and clinical data, medical history of pregnant women with preterm labour showed that in the majority of cases preterm labour had a lot of preconditions of both social and medical nature. Preterm labour occurred in employed women (79%), among which prevail (60%) office workers whose work is associated with physical inactivity and computer. Preconditions for the occurrence of preterm labour were complicated due to gestational process (36%), menstrual dysfunction (35%), infertility treatment (24%), previous reproductive loss (22%), proliferative diseases of female reproductive organs (7%). Almost all pregnant women (92%) had extragenital pathology. Among them two thirds of women (63%) had inflammatory diseases of a respiratory tract, one-third (33%) – urinary tract infections, one-fifth (20%) – vaginal infections. The combination of several infectious diseases was observed in 10 (10%) women. It should be noted that asymptomatic course of disease had 16 (16%) patients were, in 46 (46%) – exacerbation of chronic process, 63 (63%) – acute inflammation, 8 (8%) women had a complicated course. Only 57 (57%) of pregnant women received antibacterial therapy. There were no woman who

received hormonal therapy with progesterone.

Summing up the above mentioned, it can be noted that pregnant women with high risk of preterm delivery have a wide range of negative social and medical factors that is a backdrop for beginning of preterm labour. Conducted analysis of medical documentation demonstrated the important role of carrying inflammatory disease during pregnancy in initialisation of preterm delivery. Retrospective analysis of medical documentation shows that most pregnant women (92%) had inflammatory diseases of different intensity of clinical symptoms (asymptomatic, acute or chronic) during pregnancy, while only two-thirds of them received antibacterial therapy. This created favourable conditions for long-term persistence of latent infection in women's organism with possibility of its intrauterine realization.

Considering combination of different factors and preconditions (social, hormonal, infectious), which determine and launch the beginning of preterm birth, there still remains unresolved issue of choice of an efficient and effective method of treatment with a broad spectrum of influence on major pathogenetic links of this pathological process. Due to the fact that fetus is immunologically foreign for the mother organism, quite complex and not fully studied mechanisms of immune modulation aiming to save pregnancy and fetus is formed during pregnancy. The implementation of these mechanisms during physiological pregnancy is carried out with the expense of increased secretion of progesterone. After implantation, simultaneously with increasing progesterone secretion the number of progesterone receptors in myometrium increases. A sufficient concentration of progesterone and its receptor provide decreases uterine tonicity and its contractile activity. Progesterone reduces the synthesis of prostaglandins in the uterus and blocks oxytocin receptors thus it reduces the sensitivity of the myometrium to oxytocin and prostaglandin F2α. Furthermore, a sufficient progesterone level provides an appropriate ultrastructural organization of the endometrium, preventing formation of intercellular slotted connections through submitted impulses, thereby impeding reducing of the possibility of generalization of separate muscular fibers contraction in the whole uterus in response to stimuli [2, 9].

Therefore, using of natural micronized progesterone, on the one hand, is appropriate and pathogenetically reasonable, and, on the other hand, should be quite effective for treatment of threatened preterm labour against the background of the infections factor.

For confirmation of this hypothesis, at the second stage of the research we studied the efficacy of natural micronized progesterone for treatment of threatened preterm labour in pregnant women at 26-32 weeks of gestation. The efficacy of the conducted therapy was compared with similar results obtained after the conduction of the traditional therapy.

In analysing of the obstetric history of the pregnant of group I it was revealed that in the second trimester of pregnancy 17 women (30%) had acute respiratory viral infection, 11 (19%) – asymptomatic bacteriuria, 9 (16%) – nonspecific vaginitis, 7 (12%) – exacerbation of chronic pyelonephritis, 6 (11%) – acute rhino-pharyngitis, 5 (9%) – acute bronchitis, 4 (7%) – gestational pyelonephritis. At the time of admission to hospital, the women did not have any acute symptoms of infection. The women were divided into 2 groups according to received treatment. In 27 pregnant women (group 1) was used natural micronized progesterone by 100 mg twice a day sublingually during 4 weeks. The comparison group (group 2) consisted of 30 pregnant women was carried out tocolysis with calcium channel blockers in standard dose. For all pregnant women prophylaxis of fetal pneumopathy was conducted with dexamethasone (24 mg). The control group included 20 pregnant women with physiological pregnancy.

At admitting to the hospital the pregnant complained of cramping abdominal pain for the last 5.2 ± 1.1 hours. The women could not indicate specific reasons for initiating of pain. The examination noted 20 (74%) of the pregnant of group I and 21 (70%) of group II had increased uterine tone and irregular cramping abdominal pain, uterus had increased tonus respectively 5 (19%) women of group I and 7 (23%) of group II. Ultrasound examination revealed that cervical length of more than 2 cm was in 18 (67%) patients of group I and in 20 (67%) of group II, less than 2 cm, respectively, in 2 (7%) and 3 (10%) and less than 1 cm – in 2 (7%) and 3 (10%). Thus, patients with a predominance of low abdominal cramping and insignificant structural changes of the uterine cervix were included in our research that can be explained by early referring of patients to the hospital since the beginning of the disease.

The estimation of anxiety level by HAM-A showed that all patients had on average level of anxiety (21.4 ± 2.1 points). After the application of the proposed therapy the reduction of the pain intensity which patients treated with micronized progesterone had observed 25 minutes faster ($p < 0.05$) than after traditional therapy (85.2 ± 7.4 min in group I and 110.6 ± 9.8 min in group II). Simultaneously among patients of group I the anxiety level was 16.1 ± 1.8 points, corresponding to the absence of anxiety, while the patients of group II continued to be in conditions of moderate anxiety (19.3 ± 1.4 points), which, in our opinion, was due to more rapid reduction of pain syndrome.

Considering the complicated history with inflammatory diseases the level of pro- and anti-inflammatory cytokines was determined for all patients (Table 1).

Table 1: The concentration of pro- and anti-inflammatory cytokines in the blood of women with threatened preterm labour

	Control group, n=20	Group I, n=27		Group II, n=30	
		before treatment	after treatment	before treatment	after treatment
IL-2, pg/ml	1.4±0.1	5.8±0.4*	1.9±0.4	5.4±0.3*	3.0±0.3*
IL-6, pg/ml	5.3±0.5	19.2±0.6*	6.3±0.5	20.4±1.2*	14.1±0.9*
TNF-α, pg/ml	7.7±0.6	24.8±1.2*	7.5±0.9	23.4±1.0*	16.5±1.1*
IL-4, pg/ml	5.7±0.5	2.3±1.1*	6.4±0.6	2.1±0.3*	2.9±0.3
IL-10, pg/ml	4.1±0.4	1.2±0.2*	5.3±0.4	0.9±0.3*	2.6±0.3*

Note: * - indicators significantly vary relatively controls, $p < 0.05$

As our research shows that pregnant women with threatened preterm labour who have had an inflammatory process of any location, had a significant increase of level of pro-inflammatory cytokines and reduction of anti-inflammatory cytokines compared to the healthy pregnant. The application of natural micronized progesterone and traditional therapy

had a positive effect on these parameters. It was noted that patients of group I had a significant decreasing of levels of IL-2 (up to 1.9±0.4 pg / ml), IL-6 (up to 6.3±0.5 pg / ml), TNF-α (up to 7.5±0.9 pg / ml), which was not significantly different from those in the control group. Also in group I there was significant decreasing of levels of IL-4 (up to 6.4±0.6 pg / ml) and IL-10 (up to 5.3±0.4 pg / ml) which was not significantly different from those in the control group.

The decreasing of level of pro-inflammatory cytokines (IL-2, IL-6, TNF-α) and the increasing of level of anti-inflammatory cytokines (IL-4, IL-10) were noticed to the patients treated with traditional therapy but their values remained significantly different from control group and group I.

In the result of the treatment the term delivery in group I occurred to 23 (85%) women, in group II – only to 18 (60%) patients ($p<0.05$). Preterm delivery before 34 weeks occurred to 2 (7%) pregnant of group I and to 5 (17%) – of group II, at the period of 34-36 weeks to 2 (7%) and 7 (23%) women accordingly.

Thus, chronic inflammatory immune response is an important factor and trigger for the beginning of the preterm delivery. Timely prescription of 200 mg sublingual natural micronized progesterone is pathogenetically grounded because leads to reducing the level of pro-inflammatory and increasing the level of anti-inflammatory cytokines that is competitively binding to progesterone receptors and trigger of preterm labour. Increasing sensitivity of progesterone receptors of uterine smooth muscle fibers reduces tone, contractile activity and helps save pregnancy of women with chronic inflammatory diseases of different origin.

Conclusions

1. High risk pregnant women have a wide range of negative social, medical, infectious, inflammatory and other risk factors that is the background for initiation of preterm labour.
2. Chronic inflammation is launching an initial immune inflammatory response that is accompanied by insufficient secretion of endogenous progesterone and promotes the development of threatened preterm labour.
3. The application 200 mg of sublingual form of micronized progesterone is pathogenetically grounded and provides a rapid reduction of preterm labour symptoms among women with previous chronic infection.

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