© A group of authors, 2018

O.R. BAEV^{1,2}, O.N. VASIL'CHENKO¹, A.O. KARAPETYAN¹, N.K. TETRUASHVILI¹, Z.S. KHODZHAEVA¹

A COMPARISON OF TOCOLYSIS WITH NIFEDIPINE OR ATOSIBAN IN PRETERM

¹V.I.Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology of the Ministry of Healthcare of the Russian Federation, Moscow

²I.M. Sechenov First Moscow State Medical University of the Ministry of Healthcare of the Russian Federation

Aim To compare the effectiveness and safety of nifedipine and atosiban in women with threatened preterm labor. **Material and methods** The study comprised 111 pregnant women presenting with threatened preterm labor between 30 and 34 weeks of gestation, who were assigned to receive tocolysis with either nifedipine (n=54) or atosiban (n=57). The effectiveness of tocolysis was determined by the duration of pregnancy prolongation (for 48 hours, 7 days, more than 14 days). The primary outcome was the rate of pregnancy prolongation for 48 hours. The safety of tocolytics was assessed by the rate of adverse events in mothers and the neonates.

Results Tocolysis failed in eight women receiving nifedipine (14.8%) and two treated with atosiban (3.5%) (p < 0.05), and labor occurred within the first 24 hours after beginning treatment. In 46 women receiving nifedipine (85.1%) and 55 treated with atosiban (96.5%) pregnancy was prolonged for more than 48 hours (p<0.05). Among them, all births occurred more than 7 days after the initiation of tocolysis. Two women of the atosiban group underwent a second complete treatment course. Full-term births occurred in 15 (27.8%) and 19 (33.3%) women in nifedipine and atosiban group, respectively (p > 0.05%). Mean duration of pregnancy prolongation after the tocolysis with atosiban was 9.2 days longer than after nifedipine (p < 0.05). Women receiving nifedipine were more likely to have hot flushes, palpitations, dizziness and hypotension (p < 0.01) requiring a dosage reduction and increasing the interval between doses in 14.8% of cases. Eight women in the nifedipine group did not complete the tocolysis protocol due to poor drug tolerance. Of them, in five women tocolysis was ineffective, and they progressed to delivery within 24 hours after admission. After exclusion from the analysis women failing to follow the treatment protocol, no differences were found in the effectiveness of tocolysis with nifedipine and atosiban. After adjusting the groups for multiple pregnancies, the rates of singleton pregnancy prolongation for 48 hours were 88.46% and 95.56% in the nifedipine and atosiban groups, respectively, and did not differ significantly (p > 0.05). However, the duration of pregnancy prolongation was significantly longer in women receiving atosiban (29.37 \pm 14.95 days) *than nifedipine* $(20.30 \pm 11.95 \text{ days})$ (p < 0.01).

Conclusion The effectiveness of nifedipine and atosiban in pregnancy prolongation for 48 hours in threatened preterm labor is comparable. However, lower tolerability of nifedipine limits its applicability. Another advantage of atosiban is a longer period of pregnancy prolongation. Further studies are needed to clarify the effectiveness and safety of these drugs in the management of the threatened preterm labor in multiple pregnancies.

Keywords: preterm labor, tocolytics, atosiban, nifedipine.

Authors declare lack of the possible conflicts of interests.

For citations: Baev O.R., Vasilchenko O.N., Karapetyan A.O., Tetruashvili N.K., Khodzhaeva Z.S. A comparison of tocolysis with nifedipine or atosiban in preterm labor. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2018; (5): 50-6. (in Russian) https://dx.doi.org/10.18565/aig.2018.5.50-56

Premature labor has been included in the group of the great obstetrical syndromes due not only to common pathogenetic mechanisms but also because it is one of the leading causes of perinatal morbidity and mortality [1, 2]. Tocolytic therapy plays a major role in top-priority measures aimed at reducing prematurity rates. Prolongation of pregnancy with tocolysis for 48 hours has been shown to be most effective. This allows for maternal administration of corticosteroids to prevent the neonatal respiratory distress syndrome and transport to an appropriate facility for neonatal care [3].

In recent years, priorities in the use of tocolytics have gradually shifted, and in most countries, hexoprenaline and magnesium sulfate have been replaced by atosiban, the oxytocin receptor blocking agent, and the calcium channel blocker nifedipine [4, 5].

This change has been associated with a high incidence of side effects of hexoprenaline and the ineffectiveness of magnesium sulfate [6, 7]. At the same time, it remains unclear which of the currently used tocolytics has advantages in managing pregnant women with threatened premature labor.

A recently published multicentre, randomized controlled trial APOSTEL III showed similar perinatal and maternal outcomes in women with threatened preterm birth receiving tocolysis with nifedipine or atosiban [8, 9].

Nevertheless, the results of this study are inconsistent. Thus, the perinatal mortality rate in the nifedipine group tended to be higher that did not correspond to confirmed data on the sepsis incidence rate.

Conversely, the incidence of bronchopulmonary dysplasia tended to be higher in the atosiban group. In the absence of differences in the duration of pregnancy prolongation in general, after exclusion of pregnant women with premature rupture of membranes, the prolongation of pregnancy with nifedipine was an average of 10 days longer, though this was not associated with improved perinatal outcomes.

The study findings showed that side effects did not differ between groups. However, another large cohort study reported a higher incidence of hypotension and tachycardia associated with nifedipine tocolysis [10].

Considering this, comparing the efficacy and safety of nifedipine and atosiban, the most commonly used tocolytics, remain of scientific and practical interest, which was the aim of this study.

Material and methods

The study comprised 111 pregnant women presenting with threatened preterm labor between 30 and 34 weeks of gestation.

The inclusion criteria were: a satisfactory condition of the pregnant woman and fetus, unruptured membranes, gestational age between 24 and 33 weeks and 6 days, registered uterine contractions (four or more contractions 30 minutes apart and lasting 30 to 60 seconds), cervical dilation of 1 to 3 cm and a 75% cervical shortening from the baseline value, informed consent of the patient.

Exclusion criteria were: serious health conditions of the pregnant woman, requiring emergency delivery (placental abruption, severe preeclampsia, eclampsia, etc.); fetal distress; congenital fetal defects or placental abnormalities; antenatal fetal death; chorioamnionitis or other acute infections; increased sensitivity to nifedipine or atosiban.

Tocolytic therapy was initiated immediately after the diagnosis, determining gestational age, assessing fetal and maternal health, the criteria for inclusion/exclusion, assessment of contraindications the study drug. Tocolysis with nifedipine and atosiban was administered in 54 and 57 women, respectively.

The nifedipine tocolysis dosage regime:

20 mg orally, followed by 20 mg orally after 30 minutes if contractions persist, followed by 20 mg orally every 3-8 hours for 48 hours as indicated:

Or 10 mg sublingually, followed by 10 mg every 10 minutes (maximum dose for the first hour 40 mg), followed by 20 mg every 4 hours for 48 hours. The maximum dose is 160 mg /day.

The duration of tocolysis is 48 hours.

The atosiban tocolysis dosage regime. Atosiban is given intravenously in three successive stages:

- Stage 1 an initial intravenous bolus injection of 6.75 mg in 0.9 ml (1 vial) slowly injected over one minute;
- Stage 2 a continuous infusion of atosiban at a rate of 300 µg/min (18 mg/hour) up to 3 hours;
- Stage 3 a continuous infusion of atosiban at a rate of 100 µg/min (6 mg/hour) up to 45 hours.

The total duration of treatment did not exceed 48 hours. The maximum dose of atosiban for the entire course was 330 mg.

The effectiveness of tocolysis was determined by the duration of pregnancy prolongation (for 48 hours, 7 days, more than 14 days).

The assessment of the effectiveness of tocolysis included a subjective evaluation of patient's well-being during the first 3 hours, after 24 and 48 hours of the treatment. For Clinical assessment included manual palpation to evaluate resting uterine tone, frequency, and duration of contractions, fetal cardiotocography and ultrasound cervicometry to control the uterine cervix changes at 2 and 48 hours after the treatment initiation.

Clinical evaluation of newborns was conducted according to generally accepted criteria.

Statistical analysis was performed with SPSS 19.0 software.

The study was conducted within the framework of the research project "Development of clinical recommendations for the management and diagnosis of miscarriage and premature birth", approved by the Ethical Committee of the NMRC AGP.

Results

Nifedipine and atosiban groups did not differ by age (Table 1). However, in the atosiban group more women had the cardiovascular disease due to five patients with tachyarrhythmia, whereas there were no women with this condition in the nifedipine group. Also, pyelonephritis was significantly more frequent in the atosiban group (16 versus 6 cases). At the same time, anemia and low-risk thrombophilic mutations of genes was somewhat more frequent in women receiving nifedipine (4 and 8 cases, respectively) than atosiban (2 and 3 cases, respectively).

Among gynecological diseases, endometriosis (7.41 and 7.02%) and uterine myoma (7.41 and 8.8%) were most common. Overall, there were more women with gynecological diseases in the atosiban group because many of them had a history of infertility (Table 1).

Primigravida women predominated in both study groups (51.85 and 64.91%). The number of women with a history of abortions was 13 (24.07%) in the nifedipine group and 3 (3.51%) in the atosiban (p < 0.05).

The number of women with a history of abortions was 13 (24.07%) and 3 (3.51%) in the nifedipine and atosiban group, respectively (p < 0.05).

In each of the study group, 22.6% of patients had a history of early pregnancy loss. A history of two miscarriages was found in 12.96 and 10.53% women in the nifedipine and atosiban group, respectively. A history of premature births was present in 29.6 and 15.8% of women, respectively (p> 0.05).

Eleven and twenty one percent of patients achieved current pregnancy using assisted reproductive technologies (p>0.05). Among women receiving nifedipine, two patients had a dichorionic diamniotic twin pregnancy. In the atosiban group, seven, three, and two women had dichorionic diamiotic twins, dichorionic monoamniosic twins and monochorionic twins, respectively.

Therefore, multiple pregnancies were more frequent in the atosiban group.

Both groups had a similar percentage of women with the uterine scar after a cesarean section (11.1 and 10.5%).

The course of pregnancy at early gestation in women of both groups was characterized by frequent occurrence of threatened termination of pregnancy requiring treatment in a hospital (Table 2). Women of each study group often had cervical insufficiency; they received cerclage between 18 and 21 weeks of gestation.

Of the other complications of pregnancy, anemia in pregnancy (18.5 and 14.0%) and fetal growth retardation (3.7 and 14.0%) were most common. The frequency of pregnancy complications did not differ significantly between nifedipine and atosiban groups.

Gestational age at admission ranged from 28 to 34 weeks and was on average 7 days longer in the nifedipine compared with the atosiban group - 32.81 ± 1.16 (30-34) weeks versus 31.02 ± 1.44 (28-33) weeks, (p < 0.001).

According to ultrasound cervicometry at admission, the cervical length in women of the nifedipine and atosiban group ranged from 2.0 to 2.8 cm (mean 2.51 \pm 0.26 cm), and from 0.7 to 2, 8 cm (mean 2.36 \pm 0.49 cm), respectively (p <0.05).

Cervical ripening score (by Bishop's scale) ranged from 4 to 9. In pregnant women receiving nifedipine, the cervical ripening score was 5.04 ± 0.21 versus 5.35 ± 0.87 in the atosiban group (p <0.05). In the nifedipine group, women were more likely to receive prior treatment with vaginal progesterone (Utrogestan), whereas in the atosiban group more women underwent prior nifedipine tocolysis. This treatment was canceled before initiation of tocolysis.

There were no other differences between nifedipine and atosiban groups.

After the diagnosis of threatened preterm labor, all pregnant women received dexamethasone in a course

dose of 24 mg to prevent fetal respiratory distress syndrome and underwent tocolytic therapy by the above dosage regimes.

The main results of tocolytic therapy and pregnancy outcomes are shown in Table. 3

The groups differed significantly in the time needed to achieve a clinical effect. The distinct effect, subjectively determined by the patient and objectively by monitoring, was achieved earlier in the nifedipine group than in atosiban group (Table 3).

Tocolysis failed in eight women receiving nifedipine (14.8%) and two treated with atosiban (3.5%), (p<0.05). Despite tocolytic therapy, these women continued to experience regular uterine contractions resulting in cervical dilatation. Tocolysis was discontinued, and they subsequently progressed to delivery within 24 hours after admission.

In 46 women receiving nifedipine (85.19%) and 55 women treated with atosiban (96.49%), the pregnancy was prolonged for more than 48 hours (p < 0.05).

Prolongation of pregnancy for more than 7 days was achieved in 5 μ 11 women receiving nifedipine and atosiban, respectively, and for more than 14 days in 41 and 44 women, respectively, (p> 0.05).

Full-term births occurred in 15 (27.8%) and 19 (33.3%) women in nifedipine and atosiban group, respectively (p > 0.05%). Mean duration of pregnancy prolongation after tocolysis with atosiban was 9.2 days longer than after nifedipine tocolysis (p < 0.05).

Information on the duration of pregnancy prolongation in the study groups is shown in the figure.

Table 1. Demographic and clinical-anamnestic characteristics of the cohort							
Variables	Nifedipine <i>n</i> =54	%	Atosiban <i>n</i> =57	%			
Age	30.35±3.41 (25–35)		30.12±3.66 (21–38)				
Extragenital diseases:							
Cardiovascular	4	7.41*	15	26.32			
Endocrine	9	16.67	8	14.04			
Gastrointestinal	4	7.41	7	12.28			
Urinary system	6	11.11*	16	28.07			
other	12	22.22*	5	8.77			
Gynecological diseases	15	24.07*	27	47.37			

* - difference is statistically significant p<0.05.

Table 2. Features of pregnancy course							
Pregnancy complications	Nifedipine n=54	%	Atosiban n=57	%			
Threatened miscarriage							
First trimester	13	24.07	13	22.81			
Second trimester	2	3.7	6	10.53			
First and second trimester	3	5.65	9	15.79			
Cervical insufficiency	15	27.78	16	28.07			
Anemia	10	18.52	8	14.04			
Fetal growth retardation	2	3.7	8	14.04			
Polyhydramnios	0	0	2	3.51			

The great majority of pregnancies in both groups were constituted by male fetus pregnancies (64.8 and 77.2%, p > 0.05). No significant differences in the body weight of newborns were observed in the study groups, while the body length of newborns was significantly greater in the nifedipine group (p < 0.01). First-minute Apgar score ranged from 5 to 8 and did not differ significantly between the nifedipine and atosiban groups (Table 3).

It should be noted that two women in the atosiban group underwent a second complete treatment course within 24 hours.

After an initial course of tocolysis, 50.0% and 42.1% of women in the nifedipine and atosiban groups, respectively, were administered maintenance therapy with micronized progesterone (Utrogestan), 200 mg/day (at night). Besides, 19 (35.1%) and 4 (7.0%) women received maintenance therapy with magnesium sulfate, respectively (p> 0.05).

In the nifedipine group, 9 (16.67%), 9 (16.67%) and 8 (14.81%) patients experienced tachycardia, hypotension, and dizziness, respectively.

Eight women in the nifedipine group (14.8%) did not complete nifedipine tocolysis protocol because they had concurrent tachycardia, hypotension, weakness, nausea, and vomiting that required dosage reduction and increasing the interval between doses.

It should be noted that patients in this subgroup had the highest incidence of tocolysis failure - 5 out of 8 women progressed to delivery within 24 hours after admission.

The incidence of side effects in the atosiban group was significantly lower (1.75% vs. 48.15%) (p < 0.05). No cases of the study drug intolerance were observed, and all patients completed the atosiban tocolysis protocol.

After exclusion from the analysis eight women failing to follow the nifedipine tocolysis protocol, the rates of pregnancy prolongation for more than 48 hours were 93.48%, 7 days - 84.78% and 14 days - 28.26%, without significant difference between nifedipine and atosiban groups.

Considering the significantly higher proportion of multiple pregnancies in the atosiban group, we evaluated the effectiveness of tocolysis in patients with singleton pregnancies. After exclusion women with multiple pregnancies from the analysis, the nifedipine and atosiban groups comprised 52 women and 45 women, respectively.

According to the analysis, the rates of prolonging singleton pregnancy in women with threatened preterm labor for 48 hours were 88.46% and 95.56% (p>0.05) in the nifedipine and atosiban groups, respectively. The rates of prolonging singleton pregnancy for more than 7 days were 78.84 and 86.87% in the nifedipine and atosiban groups, respectively. Also, there were no significant differences in the proportion of full term births (28.85 and 35.55%). However, as before, duration of pregnancy prolongation after tocolysis was significantly longer in the atosiban group (29.37 \pm 14.95 days) compared with the nifedipine group (20.30 \pm 11.95 days) (p <0.01).

Discussion

The overall the proportion of full term births did not differ significantly between the study groups, thus confirming a lack of significant effects of tocolysis on the reduction in the rates of preterm births in general [8, 9, 11].

Nevertheless, despite the advantage of the nifedipine group over the atosiban group regarding a number



Table 3. Results of tocolytic therapy and pregnancy outcomes					
Results of tocolysis and pregnancy outcomes	Nifedipine n=54	Atosiban n=57			
The time of effect subjectively, hour #	3.26±0.57** (2–4)	2.21±0.69 (0-3)			
The time of effect objectively, hour #	3.20±0.40* (1-4.5)	2.58±0.94 (0-4)			
Number of days of pregnancy prolongation #	19.60±12.26* (0.7-49)	28.76±15.22 (1-56)			
Average gestational age at delivery, week #	35.61±1.587 (30.1–39)	35.12±2.47 (29.7-40)			
Vaginal delivery	41 (75.93%)	39 (68.42%)			
Cesarean section	11 (20.37%)	18 (31.58%)			
Vacuum extraction	2 (3.7%)	0			
Birthweight of newborns #	2614.33±336.54 (1855–3230)	2448.56±528.75 (1370–3490)			
Body length of newborns #	47.29±2.12** (43-51)	46.77±2.64 (41-50)			
First-minute Apgar score #	7.75±0.51 (6-8)	7.54±0.75 (5-8)			
Fifth-minute Apgar score #	8.68±0.57 (7–9)	8.44±0.75 (7–9)			

- data are presented as the mean ± standard deviation (minimal-maximal values). Others are absolute numbers (%).

* – difference is statistically significant p < 0.05.

** – difference is statistically significant p < 0.01.

of important indicators (the number of women with extragenital diseases, the cervical length, Bishop's cervical ripening score, the proportion of multiple pregnancies), the calcium channel blocker proved to be inferior to the blocker of oxytocin receptors in pregnancy prolongation for 48 hours.

Individual analysis of the study findings suggests that the higher incidence of nifedipine tocolysis failure was due to its poor tolerability requiring dosage reduction and increasing the interval between doses in 14.81% of patients. It was that subgroup of patients that showed the highest tocolysis failure rate. After exclusion from the analysis women failing to follow the treatment protocol, nifedipine and atosiban groups had similar rates of pregnancy prolongation for more than 48 hours. However, the number of days of pregnancy prolongation was, on average, nine days longer in the atosiban group (p <0.01).

Atosiban showed a favorable safety profile. There were no patients in this group who failed to complete tocolysis protocol. At the same time, the tocolytic effect of atosiban occurred significantly earlier and persisted longer probably due to a more effective blockade of the pathogenetic mechanism that triggers and supports uterine contraction activity.

In our study, the groups initially differed in the number of multiple pregnancies. It was therefore interesting to compare the nifedipine and atosiban groups after exclusion of women with multiple pregnancies. Comparative analysis showed similar rates of prolonging singleton pregnancy for 48 hours the nifedipine (n=52) and atosiban (n=45) groups, although there was a tendency for the higher effectiveness of atosiban (88.46% vs. 95.56%). At the same time, duration of pregnancy prolongation after tocolysis was significantly longer in the atosiban group. Unfortunately, a small number of women with multiple pregnancies did not allow a comparative analysis of the effectiveness of tocolysis with nifedipine and atosiban in this group of patients.

Conclusion

The effectiveness of nifedipine and atosiban in prolonging pregnancy for 48 hours in the management of threatened preterm labor is comparable. However, lower tolerability of nifedipine limits its applicability. Another advantage of atosiban is a longer period of prolonged pregnancy. Further studies are needed to clarify the effectiveness and safety of these drugs in the management of the threatened preterm labor in multiple pregnancies.

References

- Савельева Г.М., Шалина Р.И., Курцер М.А., Клименко П.А., Сичинава Л.Г., Панина О.Б., Плеханова Е.Р., Выхристюк Ю.В., Лебедев Е.В. Преждевременные роды как важнейшая проблема современного акушерства. Акушерство и гинекология. 2012; 8-2: 4-10. [Savel'eva G.M., Shalina R.I., Kurtser M.A., Klimenko P.A., Sichinava L.G., Panina O.B., Plekhanova E.R., Vykhristyuk Yu.V., Lebedev E.V. Preterm labor as the most important problem of modern obstetrics. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2012; 8-2: 4-10. (in Russian)]
- Ходжаева З.С., Федотовская О.И., Холин А.М. Медикаментозная терапия угрожающих преждевременных родов. Акушерство и гинекология. 2013;
 5: 17-22. [Khodzhaeva Z.S., Fedotovskaya O.I., Kholin A.M. Drug therapy for threatened preterm labor. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2013; 5: 17-22. (in Russian)]
- Locatelli A., Consonni S., Ghidini A. Preterm labor: approach to decreasing complications of prematurity. Obstet. Gynecol. Clin. North Am. 2015; 42(2): 255-74.
- Husslein P., Roura L., Dudenhausen J., Helmer H., Frydman R., Rizzo N. et al.; TREASURE study group. Clinical practice evaluation of atosiban in preterm labour management in six European countries. BJOG. 2006; 113(Suppl. 3): 105-10.
- Jørgensen J.S., Weile L.K., Lamont R.F. Preterm labor: current tocolytic options for the treatment of preterm labor. Expert Opin. Pharmacother. 2014; 15(5): 585-8.
- Crowther C.A., Brown J., McKinlay C.J., Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst. Rev. 2014; (8): CD001060. doi: 10.1002/14651858.CD001060.pub2.
- Neilson J.P., West H.M., Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst. Rev. 2014; (2): CD004352. doi: 10.1002/14651858. CD004352.pub3.
- van Vliet E.O.G., Nijman T.A.J., Schuit E., Heida K.Y., Opmeer B.C., Kok M. et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. Lancet. 2016; 387(10033): 2117-24. doi: 10.1016/S0140-6736(16)00548-1.
- Nijman T.A.J., Goedhart M.M., Naaktgeboren C.N., de Haan T.R., Vijlbrief D.C., Mol B.W. et al. The effects of nifedipine and atosiban on perinatal brain injury: a secondary analysis of the APOSTEL III trial. Ultrasound Obstet. Gynecol. 2017; April 28. doi: 10.1002/uog.17512
- de Heus R., Mulder E.J., Derks J.B., Visser G.H. The effects of the tocolytics atosiban and nifedipine on fetal movements, heart rate and blood flow. J. Matern. Fetal Neonatal Med. 2009; 22(6): 485-90.
- Баев О.Р., Васильченко О.Н., Карапетян А.О., Тетруашвили Н.К., Ходжаева З.С. Сравнение токолиза гексопреналином и атозибаном. Медицинский совет. 2017; 2: 57-61. [Baev O.R., Vasil'chenko O.N., Karapetyan A.O., Tetruashvili N.K., Khodzhaeva Z.S. Comparison of tocolysis with hexoprenaline and atosiban. Meditsinskii sovet/Medical Council. 2017; 2: 57-61. (in Russian)]

Received 08.12.2017 Accepted 22.12.2017

Authors' information:

Address: 117997, Russia, Moscow, Academician Oparin St., 4. a_karapetyan@oparina4.ru

Baev Oleg Radomirovich, Dr.Med.Sci., Professor, Head of the Maternity Department, V.I. Kulakov NMRC AGP of the Ministry of Healthcare of the Russian Federation. Address: 117997, Russia, Moscow, Academician Oparin St., 4. E-mail: o_baev@oparina4.ru

Vasil'chenko Oksana Nikolaevna, Ph.D., Senior Researcher at the Maternity Department, V.I. Kulakov NMRC AGP of the Ministry of Healthcare of the Russian Federation. Address: 117997, Russia, Moscow, Academician Oparin St., 4. E-mail: o_vasilchenko@oparina4.ru

Karapetyan Anna Ovikovna, аспирант at the Maternity Department, V.I. Kulakov NMRC AGP of the Ministry of Healthcare of the Russian Federation.

Tetruashvili Nana Kartlosovna, Dr.Med.Sci., Head of the 2nd Obstetrics Department of Pregnancy Pathology, V.I. Kulakov NMRC AGP of the Ministry of Healthcare of the Russian Federation. Address: 117997, Russia, Moscow, Academician Oparin St., 4. E-mail: n_tetruashvili@oparina4.ru

Khodzhaeva Zul'fiya Sagdullaevna, Dr.Med.Sci., Professor, Head of the 1st Obstetrics Department of Pregnancy Pathology, V.I. Kulakov NMRC AGP

of the Ministry of Healthcare of the Russian Federation. Address: 117997, Russia, Moscow, Academician Oparin St., 4. E-mail: z_khodzhaeva@oparina4.ru