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Premature Birth is an Unsolved Problem of the 21st Century

Sarkisova L. V.
Bukhara State Institute named after Abu Ali IbnSina

Abstract: The problem of preterm birth is one of the urgent medical and social problems in obstetrics. Despite significant progress in the development of new tocolytic drugs, the incidence of preterm birth does not show a clear downward trend. The article presents the results of scientific research on the inhibition of spontaneous contractile activity of the uterus during preterm birth, which increases the chances of survival of the newborn.
Atosiban is the first drug specifically designed to suppress labor. Comparing it with other drugs with a tocolytic effect, it was shown that in terms of efficacy, safety and tolerability, atosiban is not inferior, but superior to them in the treatment of pregnant women with threatened preterm birth.

Keywords: atosiban, oxytocin receptor blocker, preterm birth.

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide, with most deaths occurring in newborns less than 32 weeks' gestational age. [1,3]. In general, 15 million cases of preterm birth are recorded annually worldwide. The frequency of rupture of membranes in preterm pregnancy ranges from 40-50% of all preterm births. [2,4] The problem of preterm birth is one of the urgent medical and social problems in obstetrics. Despite significant progress in the development of new tocolytic drugs, the incidence of preterm birth does not have a clear downward trend. Clinical studies by I. Usta et al. tocolytics, as well as other preventive programs over the past 40 years, their number does not tend to decrease.

It should be noted that every second child who survived at 22–26 weeks of gestation has impaired motor and sensory functions by 2.5 years of age. Premature birth, as well as timely, is characterized by the development of contractile activity of the uterus. As you know, one of the most popular stimulants of uterine contraction is oxytocin. During pregnancy, oxytocin is produced not only in the hypothalamus, but also in the decidual tissue, and its concentration increases at the end of pregnancy and on the eve of childbirth.

P. Arthur and co-authors [4.10,12] note that the oxytocin receptor is a protein associated with phospholinase and the attachment of oxytocin to the receptor leads to its activation. As a result, the content of inositol triphosphate and diacylglycerol increases. N.Vrachnis and co-authors [2,9,13] noted in their studies that inositol triphosphate activates specific receptors of the sarcoplasmic reticulum with the release of calcium (Ca2+) into the cytosol, which, in turn, also induces calcium influx from the extracellular space. Rho kinase, which inhibits myosinphosphatase, is involved in the implementation of this mechanism.

As noted by A. Fuchs et al. [14,15], oxytocin promotes the production and release from the decidual tissue and fetal membranes of other activators of uterine contractile activity - prostaglandins E and F.As for the increase in the concentration of oxytocin on the eve of childbirth, it can be of both fetal and maternal origin.There fore, O.Baev et al. [11] note thatinhibition of contractile activity of the uterus in preterm pregnancy increases the chances of survivalnewborn, as well as oxytocin is an induceruterine contraction, suppression of its activity

is main goal at premature child birth. Melin et al. [32] back in the 1980s, after changes in positions 1, 2, 4, and 8 of the oxytocin structure, analogs with a high degree of affinity for myometrial receptors were obtained.And then Akerlund et al [18] noted that two of them, differing from the others in position 4, had the ability to suppress vasopressin-induced myometrial contractions. This ability was the most pronounced at atosibana ,that's why R.Lamont ,K.Kam[3]choseit for further research and clinical applications at dysmenorrhea and premature child birth.

Nanetti and co-authors [4,5], studying the molecular mechanisms and safety of using atosiban ,found thatthat during incubation with oxytocin, the level of nitric oxide in cellstropho blast decreases.

Atosiban in insignificant amounts crosses the placental barrier. Valenzuela et al. [16,17,19] indicate that after administration of atosiban at a rate of 300 μg/min, the ratio of its concentration in the fetal body and the concentration of atosiban in the mother's body is 0.12, regardless of the duration of the infusion. . In experimental studies by P.Greig and co-authors [9,11,12,8,20], it was found that atosiban did not affect blood pressure and blood gas composition. Conducted pharmacokinetic studies illustrate that the minimum effective bolus dose of atosiban is 2 mg. R. Lamont and K. Kam [3] found that the clinically effective dose of continuous intravenous infusion is 300 μg/min. This volumetric rate of administration of the drug provides a concentration of 450 ng / ml, which is sufficient to saturate the uterine receptors. A bolus dose of 6.75 mg immediately provides a state of uterine rest, which is then maintained by continuous intravenous infusion. In a blinded, placebo-controlled study, it was shown that, compared with placebo, in 77% of cases in pregnant women with preterm labor, atosiban caused a more marked decrease in the frequency of uterine contractions. In clinical studies conducted with T. Good winan dco-authors[21]noted what at this efficacy was higher in patients with a gestational age of more than 28 weeks, reaching statistical significance after 32 weeks. Complete cessation of uterine contractions was found in 26% of patients, while in the placebo group only 6% ($p<0.05$). Results of this study testify what perinatal mortality in the atosiban group was higher, the authors [21,22] explain that this is conditioned more high percent female patients in gestational age up to 26 weeks , which were included in this group. Strict criteria were used to establish the diagnosis of preterm labor: the number of contractions at least 4 times in 30 minutes, lasting at least 40 seconds, opening of the cervix during vaginal examination from 1 to 3 cm and shortening by 75% or opening of 3 cm and shortening by 50% or an increase in cervical dilatation by 1 cm and / or shortening by 50% on re-examination. Quantity female patients which did not give birth within 24.48 and 168 hours from the start of treatment, there were reliably more in group receiving atosiban .This relationship was most clearly observed after28weekspregnancy[eleven]. P. Husslein and co-authors [5,22.23] note that the these countries study efficiency to sibana ,independenciesfromselectedcriteriaforstarttreatment,hesitatedfrom78.1%before89.9%.
Researchers M.wuandco-authors [24] submitted comparative description observation, where at osibanwas applied at female patients With prematuregapmembranes of one fetus from twins, which threatenedpreterm birth at 22 weeks gestation .

Tocolys is atthreaten in gpremature child birth pursues the main goal: to provide a period of time for the prevention of respiratory distress syndrome new born. Therefore, it is important to know what possibilities drugs, providing preventionrespiratorydistress syndrome new born on the the period,-this is glucocorticoids ,which willto interactWith drug stocolysis .

Atosiban was always administered according to the recommended regimen, whereas in the beta-mimetic group, after the administration of a placebo bolus dose, treatment was carried out in accordance with the recommendations adopted in each particular institution [3,6,11].

The results of the study indicate that the effectiveness of atosiban and beta-mimetics in prolonged pregnancies at 48 and 168 hours did not differ significantly and amounted to 90%

and 80%, respectively. There were no differences in the frequency of perinatal losses and morbidity. But at the same time, additional tocolytic therapy was significantly less frequently required in the atosiban group, 37% vs. 47%, respectively ($p<0.01$). As a result, taking into account the percentage of patients in whom therapy was effective in accordance with the main protocol (no delivery within 168 hours without additional treatment), atosiban was more effective than beta mimetics, 59.6% vs. 47.7% ($p = 0.0004$).

L. Driul and co-authors [6,28] also noted a lower incidence of side effects of atosiban compared to beta mimetics. A study conducted in Korea by J. Shim et al. [29] also showed the tocolytic efficacy of atosiban in prolonging pregnancy by 168 hours, 60.3%, while that of ritodrine was only 34.9%. But nevertheless, the authors did not reveal differences in the prevention of childbirth during the first 48 hours of therapy. As for the frequency of side effects, it was significantly less in the group of patients treated with atosiban, 7.9% versus 7.8% ($p=0.0001$). A comparative study on the use of atosiban and nifedipine in the treatment of threatened preterm labor by R. De Heus et al. [31], R. Salim et al. 3% respectively. However, W. Al Omari et al. [34] noted that atosiban was more effective in patients with a history of preterm labor, while nifedipine showed better results before 28 weeks' gestation. In addition, the effect of nifedipine was faster, on average after 2.2±0.93 hours versus 4.2±1.1 for atosiban. The results of studies [33] indicate that atosiban was more effective than nifedipine in the first 48 hours of treatment (68.6 vs. 52%, $p = 0.03$), while nifedipine had a longer effect and after 168 hours, i.e. 7 days, the percentage of saved pregnancies was 78.6 and 89.3, respectively ($p=0.02$).

As a result, the average gestational age at the time of delivery was 35.2±3.0 and 36.4±2.8 weeks ($p=0.01$). In the conducted studies, it appears that the frequency of adverse reactions in the group of patients treated with nifedipine was higher. The analysis of the conducted studies showed that

A characteristic distinguishing feature of atosiban compared to other tocolytics is a well-defined regimen of use, calculated on the 48 hours necessary for the prevention of fetal respiratory distress syndrome.

V. Flenady et al [8.35] note that a systematic Cochrane review found no benefit of atosiban versus placebo, beta mimetics, and calcium channel blockers in terms of pregnancy prolongation or fetal outcome. But at the same time, this study showed a significantly lower incidence of side effects with atosiban (RR 0.38, 95%, G10.21 vs. 0.68). It should also be taken into account that the effectiveness of the drug is influenced by the criteria for establishing the diagnosis and determining the indications for its appointment, which was not taken into account in the systematic review.

Currently, in the selection of multiple publications, only one study was found on the use of atosiban for the purpose of maintenance therapy after the main course. As noted by G. Valenzuela and co-authors [23,32], while atosiban was used by continuous subcutaneous infusion using a pump at a rate of 30 μg/min until the end of 36 weeks of pregnancy.

This maintenance treatment with atosiban was associated with an increase in latency to 32.6 days compared to 27.6 days for placebo ($p = 0.02$). However, D. Papatsonis, V. Flenady, H. Liley (2013)

[33] - The authors of a Cochrane review based on this single study reported that this approach did not reduce the incidence of preterm birth and there is insufficient evidence to recommend atosiban, like other tocolytics, for maintenance therapy in preterm birth. R. Lamont, K. Kam [3] note that atosiban was approved and introduced into clinical practice by medical institutions of the European Community in 2000 and is currently used in more than 70 countries. Over the past 12 years, there has been a clear trend to replace beta mimetics, which dominated as tocolytic therapies, with calcium channel blockers and atosiban.),

J. Jorgensen et al. (2014) [34, 35] consider atosiban the drug of choice for preterm spontaneous labor. J. Wex et al. [26] conducted a clinical and economic analysis of the effectiveness of using beta-mimetics during treatment (monitoring of hemodynamic parameters, glycemia, fluid balance), the frequency of adverse reactions, and the need to refuse treatment. The results of the analysis show that atosiban saves more than 400 euros for the treatment of this patient in Germany. A similar study was conducted in Italy, which showed an even higher economic feasibility of replacing beta-mimetics with atosiban [27]. Thus, large studies and sufficient accumulated experience in the use of atosiban justify its use as the most optimal drug for maintenance therapy in threatened preterm labor.

REFERENCES:

1. Veropotvelyan P.N., Narytnik T.T., Veropotvelyan N.P. Features of the course of pregnancy and early preterm labor at 22–27 weeks //Medical aspects of women's health. - 2013. - No. 7.
2. Veropotvelyan N.P., Veropotvelyan P.N., Volenko N.V., Walk Yu.S. A modern view on placental dysfunction in patients suffering from premature termination of pregnancy // Women's Health, 2012, No. 1 (67). – P. 68–74.
3. DobrokhotovaYu.E., Jobava E.M., Stepanyan A.V., SudakovaG.Yu. Micronized progesterone in the treatment of threatened preterm birth: a systematic review and meta-analysis of randomized and controlled trials. // Issues of gynecology, obstetrics and perinatology. - 2019. - V. 9, No. 4. - S. 63-70.
4. Kozlov P.V. Etiology and pathogenesis of premature rupture of membranes in preterm pregnancy. // Issues of gynecology, obstetrics and perinatology . - 2017. - Volume 6, No. 2. - S. 64-72. Sarkisova L. V. Morphological features of the placenta in preterm birth // Problems of biology and medicine. - 2012. - T. 1. - S. 166.
5. Sarkisova L.V. Features of the clinical course of preterm labor and perinatal outcomes// Collection of materials of the first Bukhara international conference of medical students and youth.2019. -S. 262-263.
6. Sarkisova L. V. Analysis of the risk of preterm birth by assessingpolymorphism of tumor necrosis factor alpha and interleukin 1-beta //Biology and Integrative Medicine. – 2021. – no. 2 (49). - S. 104-117.
7. Sarkisova L. V. et al. Modern aspects of the treatment of pregnant women with gestosis , based on changes in central hemodynamics // Russian Bulletin of the obstetrician-gynecologist. - 2003. - no. 4. - P. 56.
8. Sarkisova L. V. et al. Modern aspects of the treatment of pregnant women with preeclampsia, based on changes in central hemodynamic parameters // Russian Bulletin of the Obstetrician-Gynecologist. - 2003. - no. 4. - S. 56.
9. Fedotovskaya , O.I. Modern approaches and prospects for determining the risk of preterm birth / O.I. Fedotovskaya , Z.S. Khodzhaeva, A.E. Donnikov // VI International Congress on Reproductive Medicine: materials of the Congress. - Moscow, 2016. - S. 324
10. Khodjaeva, Z.S. Drug therapy of threatening preterm labor (literature review) / Z.S. Khodzhaeva, O.I. Fedotovskaya , AM Kholin // Obstetrics and Gynecology. - 2016. - No. 5. - S. 17-22.
11. Arthur P., Taggart MJ, Mitchell BF Oxytocin and parturition: a role for increased myometrial calcium and calcium sensitization, Front. biosci . 20 17 12:619–33.
12. Akerlund M., CarlssonAM, Melin P., Trojnar J. The effect on the human uterus of two newly developed competitive inhibitors of oxytocin and vasopressin. Actaobstet .Gynecol

. Scand.2020 64: 499–504.

13. Baev OR, Kozlova OA, Tysyachnyi OV, Usova EA The use of oxytocin receptors blocking agent atosiban to suppress spontaneous labor. Am. J. Obstet. Gynecol. 2015 1:5–117
14. Baskett TF The development of oxytocic drugs in the management of postpartum haemorrhage . Ulster Med. J. 201 4 Suppl .: 2–6.
15. Du Vigneaud V., Ressler C., Trippett S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. J Biol. Chem. 1953 205: 949–57
16. Finnstrom O., Olaussen P.O. , Sedin G., Serenius F., Svenningsen N., Thiringer K. Et al. The Swedish national perspectives study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. Actapaediatr . 1999 86: 503–11.
17. Fuchs AR, Husslein P., Fuchs F. Oxytocin and the initiation of human parturition. II. Stimulation of prostaglandin production in human decidua by oxytocin. Am. J. Obstet. Gynecol. 2000 141(6): 694–7.
18. Greig PC, Massmann GA, Demarest KT, Weglein RC, Holland ML, Figueroa JP Maternal and fetal cardiovascular effects and placental transfer of the oxytocin antagonist atosiban in late gestation pregnant sheep. Am. J. Obstet .Gynecol2020. 169(4): 897–902.
19. Goodwin TM, Valenzuela G., Silver H., Hayashi R., Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban . Am. J. Perinatol .2016 13 (3): 143–6.
20. Helmer H., Brunbauer M., Rohrmeister K. exploring the role of Tractocile in everyday clinical practice. Br. J.
21. Lamont RF, Kam KYR Atosiban as a tocolytics for the treatment of spontaneous preterm labor. Expert Rev. Obstet. Gynecol. 20 18 3(2): 163–74.
22. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C. GAPPS Review Group. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth. 2010 10 (Suppl. 1): S1–22. Available at: http://www.biomedcentral.com/1471 2393/10/S1/S1
23. Nour NM Premature delivery and the millennium development goal. Rev. obstet. Gynecol. 2012 5 (2): 100–5.
24. Nanetti L., Raffaelli F., Giulietti A., Sforza G., RaffaeleGiannubilo S., Ciavattini A. et al. Oxytocin, its antagonistatosiban , and preterm labor: a role for placental nitric oxide. J. Matern . Fetal Neonatal Med. 2014 Jul 11:1–6.
25. Obstet. Gynaecol . 2003 110 (Suppl. 20): 113–5.
26. Romero R., Sibai BM, Sanchez Ramos L., Valenzuela GJ, Veille JC, Tabor B. et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: A randomized, doubleblind , placebocontrolled trial with tocolytic rescue. Am . J. Obstet. Gynecol. 2000 182: 1173–83.
27. Sanu O., Lamont RF Critical appraisal and clinical utility of atosiban in the management of preterm labor. Ther .Clinic .riskManag . 2010 6:191–9.
28. Serov VN, Salov IA, Burlev VA, Marinushkin DN The role of fetal oxy tocin induction of uterine activity. Russian Gazette obstetriciangynecolo gist. 2001 1 :15–8.
29. Sarkisova LV, Morphological features of placentas in preterm labor //Problems of biology

and medicine. - 2012. - Vol. 1. - P. 166.LITERATURE FOR CITATION

30. Sarkisova LV, Mukhtorovna KG, Kobylovna ES Premature Birth In A Modern Aspect //International Journal of Bio-Science and Bio-Technology. - 2019. - Vol. 11. - No. 10. - pp. 31-37
31. Usta IM, Khalil A., Nassar AH Oxytocin antagonists for the management of preterm birth: a review. Am.J. _ Perinatol . 2011 28 (6): 449–60. Doi : 10.1055/s00301270111.
32. Vrachnis N., Malamas FM, Sifakis S., Deligeoroglou E., Iliodromiti Z. The oxytocinoxytocin receptor system and its antagonists as tocolytic agents. Int. J. Endocrinol . 2011 2011: Article ID 350546. Doi:10.1155/2011/350546
33. Valenzuela GJ, Craig J., Bernhardt MD, Holland MI Placental passage of the oxytocin antagonist atosiban . Am. J. Obstet. Gynecol. 1995 172 (4, Pt 1): 1304–6.
34. Wood N., Marlow N., Costeloe K., Chir B., Gibson A., Wilkinson A. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N. Engl. J. Med. 2000 343: 378–84.
35. Woodcock N., Taylor C., Thornton S. Effect of oxytocin receptor antagonist and rho kinase inhibitor on the Ca ++ sensitivity of human myometrium. Am. J. Obstet. Gynecol. 20 14 190: 222–8.
36. Shamsievna R. G. Modern Aspects of Studying the Features of Morphofunctional Characteristics of Testes under Various Factor Influences //Eurasian Scientific Herald. – 2022. – T. 7. – C. 279-286.
37. Sh R. G. Experimental modelling of traumatic brain injury in white rats //Тиббиётда янги кун. – 2021. – Т. 2. – №. 34. – С. 197-200.