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Утеротонические препараты в профилактике и лечении акушерского кровотечения

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Одной из основных причин материнской смертности являются акушерские кровотечения, среди которых $^2/_3$ случаев приходится на кровотечения в раннем послеродовом периоде. Существующие методы профилактики и остановки маточного кровотечения в послеродовом периоде не всегда позволяют добиться желаемого результата ввиду неэффективности предпринимаемых мер. Цель исследования состояла в изучении эффективности утеротонических препаратов в профилактике и лечении акушерских кровотечений. Проведен детальный систематический анализ современной отечественной и зарубежной литературы, посвященной использованию утеротонических препаратов, рассмотрению основных показателей препаратов, применяемых для профилактики и остановки акушерского кровотечения. В исследовании использованы такие информационные базы, как eLIBRARY.RU, Scopus, PubMed, MEDLINE, ScienceDirect, Cochrane Library, с момента создания до декабря 2020 г. Несмотря на значительное количество исследований утеротонических препаратов, в настоящее время не разработаны методы, обладающие абсолютной лечебной эффективностью, в связи с чем необходимо проведение изысканий по разработке новых лекарственных средств на основе их синтетических аналогов.

Ключевые слова: послеродовое кровотечение; утеротоники; окситоцин; мизопростол; алкалоиды спорыньи; побочные эффекты.

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Uterotonic drugs in obstetric bleeding prevention and treatment

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One of the main causes of maternal mortality is obstetric bleeding, among which 2/3 of cases are bleeding in the early postpartum period. The existing methods of preventing and stopping uterine bleeding in the postpartum period do not always allow achieving the desired result due to the ineffectiveness of the measures taken. The aim of this study was to assess the effectiveness of existing uterotonic drugs in the obstetric bleeding prevention and treatment. We performed a detailed systematic analysis of modern domestic and foreign literature on uterotonic drugs being used to prevent and stop obstetric bleeding, with their main parameters considered. The study used such information databases as eLIBRARY.RU, Scopus, PubMed, MEDLINE, ScienceDirect, and Cochrane Library from inception to December 2020. Despite a significant number of studies devoted to exploring the possibilities of uterotonic drugs, currently there are no methods with absolute therapeutic efficacy, which requires research to develop new drugs based on their synthetic analogues.

Keywords: postpartum hemorrhage; uterotonics; oxytocin; misoprostol; ergot alkaloids; side effects.

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INTRODUCTION

According to the World Health Organization (WHO), postpartum hemorrhage (PPH) accounts for about 25% of the total number of maternal deaths worldwide [1]. In most cases, the etiological factors of this pathological condition are hypotonia and atonia of the uterus, which occur as a result of the irrational use of certain medicines, such as the following: uterotonics, sedatives, analgesics, tocolytics, ganglioblockers, etc. [2]. The possible risk of developing PPH significantly increases in patients with placenta, retention of placenta or parts of the uterus, and women with multiple pregnancies, macrosomy of the fetus, multi-water, or post-obstetric surgery [3, 4].

The active management of the third stage of childbirth involves the use of uterotonic drugs (UTDs) for the prevention and treatment of PPH. For the third period of childbirth, WHO specialists recommend the use of medicines that have a detotonic effect on the uterus, such as the following: oxytocin (OX), carbetocin (CBT), analog prostaglandin E_1 (misoprostol (MSP)), preparations of *secale cornutum* (ergometrine and methylergometrine (MEM), and various combinations of OX with other uterotonics [5]. The types of medicine used for the exposure of myometrium can be divided into two groups: medicines that increase the tone and contraction of myometrium (OX, CBT, and MSP) and those that mainly increase the tone of myometrium (ergometrine).

With active tactics of the third stage of childbirth, UTDs reduce the risk of obstetric bleeding by 60% [2, 4]. However, the question on the safety and effectiveness of each medicine, which are associated with side effects and contraception that can lead to complications that develop after their use, remains open due to the lack of clear indications, effective ways of injection, optimization of doses, and duration of administration. To date, scientists around the world are conducting active research aimed at the development and study of the pharmacological properties of uterotonics, the identification of indications and contraindications for use, and the search for the best ways and duration of the introduction of these drugs.

The present study aimed to investigate the effectiveness of UTDs in the prevention and treatment of obstetric bleeding. A detailed systematic analysis of modern domestic and international literature on the use of UTDs was carried out with consideration of the main indicators of medicines used to prevent and stop obstetric bleeding. The study used information from bases, such as eLIBRARY.RU, Scopus, PubMed, MEDLINE, ScienceDirect, and Cochrane Library, from their inception until December 2020.

Analysis of the effectiveness and conditions of OX

OX is one of the main medicines recommended by WHO for the prevention and treatment of obstetric bleeding. OX was first synthesized by the American biochemist Vincent du Vigneaud, who established an OX amino acid sequence, in 1953. The exogenous OX is structurally identical to endogenous OX and is a nonapeptide hormone consisting of nine amino acids (Cys-Tyr-Ile-Gln-Asn-Cys-Cys-Pro-Leu-Gly-NH_2) with a sulfur bridge between two cysteines. Structurally, this compound is similar to another nonapeptide of the vasopressin family, with a difference of two amino acids [6]. The synthesis of OX occurs at the level of paraventricular and supraoptic nucleus of the hypothalamus, and its accumulation occurs at the level of neurophysis. In a woman's body before childbirth, endogenous OX is also synthesized in the decidual membrane, amnion, placenta, and chorion. From the cells of these tissues, OX, together with the amniotic fluid, reaches the uterus, where it increases its contractile activity.

OX exerts its pharmacological effect (uterine effect) by activating OX uterine receptors (OURs) [7]. Before childbirth, the number of OUR increases by 300 times in comparison with their number in non-pregnant women [8]. With the spontaneous 11th birth at the preterm period of pregnancy, the number of OURs increases by 2–2.5 times. In small doses, OX can increase the frequency and amplitude of uterine contractions, whereas in large doses, it increases the tone of the uterus and strengthens and increases its contractions [9, 10]. These effects are implemented by three different mechanisms involving a family of rhodopsin receptors associated with G-proteins (Gαq-protein in myometrium). The number of OURs in the uterus is heterogenic: the highest concentration is determined in the area of the uterine floor, whereas the number of receptors is considerably lower in the body and lower segment of the uterus. The degree of expression of OURs depends on the period of ancestral activity. The maximum density of OURs is typical for the onset of childbirth, and the minimum is commonly observed at the beginning of the second period [10–12]. This condition is important for understanding the differences in the effects of OX in relation to its use in the prevention of PPH during a planned or emergency cesarean section during childbirth, specifically when the drug has already been used. OX is characterized by a short half-life (1–10 min), which necessitates its long-term infusion; however, its continuous and long-term administration is accompanied by the desensitization of OURs, which contributes to the development of various complications. S. Robinson and co-author (2003) exposed myometrium tissue to a highly concentrated OX solution, resulting in a loss of sensitivity in 50% of cells after 4.2 h [13]. This effect is often observed in the weakening of ancestral forces, which often leads to a significant increase in the risk of developing PPH [6, 10–12]. The desensitization of OURs becomes dangerous in an emergency cesarean section when the woman had previously received OX [13]. In literary sources, the neuropeptide OX is described not only as

a mediator of contractile activity of the uterus but also as a factor that plays an important role in the social activity of people with various psychological and physical symptoms and conditions [14]. The decrease in the effectiveness of OX against the background of the desensitization of OURs has led to studies searching for the best injection patterns that will not result in a decreased sensitivity of uterine receptors. The authors suggested that myometrium remains more sensitive to OX when applied intermittently than with its long-term and continuous effects. Thus, intermittent infusion is effective in solving the problem on PPH. However, the issues of dose, duration, and delivery pathways should be studied in further detail [15, 11, 17].

According to WHO recommendations, 10 IU OX should be administered intramuscularly or intravenously for the prevention of PPH in the third period of childbirth [5]. However, the manner of its introduction remains unresolved. Intravenous OX more effectively reduces the amount of blood loss and the likelihood of bleeding in comparison with intramuscular administration. A feature of this pathway of introduction is the low frequency of side effects [18–21].

T. Pantoja and co-author (2003), by studying the efficacy and safety of OX to prevent PPH, concluded that the effectiveness of using OX to prevent blood loss of 1000 ml is questionable; however, the effectiveness of administration has been confirmed for the 500 ml volume [22]. The side effects must be considered when prescribing OX; the most significant and dangerous of these effects are the changes in the cardiovascular system (CVS) of the woman giving birth. E.N. Degtyareva and co-author (2018) showed that with the introduction of OX at a dose of 10 IU, the risk of developing ischemia manifests in the form of depression of segment ST by more than 0.5 mm, and the birth rate increases by 36 times compared with that at a dose of 5 IU [20]. OX can cause peripheral vasodilation and increase cardiac output [21]. In addition, undesirable drug reactions from hemodynamics are amplified in the conditions of neuraxial anesthesia and are directly related to the reduction of compensatory reflex reactions of the body of the mother [21]. Thus, the use of OX in women with cardiovascular pathology is associated with a high risk of cardiovascular complications and and an individual approach is needed.

The excessive dose of 10 IU was demonstrated in a study conducted by a group of scientists in 2018. The results provided the basis for the "rule of threes," which consists of three-fold introduction of 3 IU OX every 3 min [23]. This rule is especially important in the case of prompt delivery, which requires the long-term introduction of OX in the form of infusion [23]. The "rule of threes" refers to the introduction of 3 IU shock dose, followed by the assessment of the condition after 3 min and the administration of two rescue doses at 3 IU. The three doses are administered as one "strike" and two "dose of rescue." The supporting dose of 3 IU is diluted in 100 ml saline solution and injected within an hour [24].

American clinicians consider the "rule of threes" to be the best way to use OX in routine and emergency early delivery and recommend it for clinical practice [25, 26]. Importantly, the use of this technique with reduced dosage causes no effect on the amount of blood loss and hemodynamic rates of the woman giving birth.

Among the side effects of OX is its vasopressin-like action, which is the greatest risk in the case of the development of PPH and occurs when a large amount of fluid is injected in parallel to replenish blood loss. As a result, the patient may develop hypervolemic complications with the onset of acute pulmonary edema [8]. The irrational use of OX with the hyperstimulation of myometrium can lead to the development of hypoxia and fetal asphyxia followed by intrauterine death [25]. With the use of OX, nausea, vomiting, heart rhythm disorders, hypertonus of the uterus and its rupture, discoordinated or excessively strong birth activities, and various allergic reactions may also occur [26]. OX has a number of obstetric contraindications, including the following: transverse and oblique fetal position, facial position of the fetus, the presence of scar on the uterus as a result of surgical interventions (cesarean section and myomectomy), the risk of uterus rupture due to overexposure resulting from multiple pregnancies and births, more than four births in history, the pre-birth of the placenta and/or blood vessels, severe preeclampsia or eclampsia, chronic renal failure, invasive cervical carcinoma, pervasive umbilical cord, fetal distress, and hypersensitivity to OX [27].

In addition to obstetric contraindications and side effects, OX may cause long-term effects, among which postpartum depression is the most common. The symptoms can manifest as early as 2–4 days after childbirth and persist from several days to several months. According to researchers, these symptoms can be observed in about 80% of new mothers, but the mechanism of their occurrence is not fully studied [27].

The efficiency of OX in the generation of uterine contraction is influenced by various external and internal factors, among which compliance with storage conditions is important. The optimal storage temperature is between 2 °C and 8 °C [28, 29]. The volatility of OX under the influence of high temperature confirms the results of a number of studies, which have shown that one third of samples in violation of storage conditions failed to meet the quality standards in terms of the content of the active substance and efficiency, which are significantly reduced in the case of non-compliance with the cold-chain storage conditions. In 2018, a group of American scientists developed freeze-dried tablets for sublingual use; the active substance in these tablets can remain active at a temperature of 40 °C [30, 31]. The effect is achieved by the bacteriostatic agent

chlorobutanol, which can have a stabilizing effect on the oxy molecule, which gives drug resistance to the effects of temperature up to 80 °C; however, the stabilization mechanisms should still be studied [32]. In accordance with WHO recommendations, as the first line of prevention for hypotonic bleeding during cesarean section, OX should be combined with other uterotonics, including MEM and MSP (evidence level A) [33].

Analysis of the effectiveness and conditions of CBT

The shortcomings of OX have led to the development of CBT, which is a long-acting synthetic analog of OX. A stable chemical form provides it with a long half-life (40 min), which allows the introduction of this drug once [34]. The pharmacological effects of CBT are similar to those of OX and are mediated by the activation of OUR in the myometrium. However, certain differences exist: the reductions in myometrium caused by the introduction of CBT have a greater frequency and amplitude than those caused by the introduction of OX [35]. If the use of CBT was preceded by the use of OX, the uterotonic effect of the first will be reduced due to the desensitization of OURs in the myometrium [36].

According to the Cochrane network meta-analysis of seven studies conducted in 2018 involving more than 2,000 patients, compared with OX, CBT is a more effective drug for the prevention of PPH in cesarean section [37]. The authors noted decreases in the incidence of PPH, need for other UTPs, and frequency of hemotransfusion. The results of the triple-blind randomized control trial showed that the intravenous pathway of CBT is more effective in the prevention of PPH in normal vaginal births with a homogeneous high-risk single pregnancy than intravenous OX [38].

However, despite the potential benefits of the synthetic equivalent of OX, according to WHO recommendations (2018), the use of CBT is limited only to the prevention of PPH during cesarean section. This limitation is possibly due to its higher cost, which is about 10 times that of OX. In addition to cost, the safety OX use is important, especially in the absence of the ability to significantly influence the activities of CVDs [39, 40]. According to A.G. Babloyan and co-author (2019), the data are insufficient to confirm the safety of CBT use during cesarean section in women with comorbidities, including CVD diseases [41].

One of the contraindications to the application of CBT is the prohibition of its use directly during pregnancy, childbirth, and until birth or extraction of the child; in the Russian Federation, the drug is used to prevent atonic bleeding during cesarean section under spinal or epidural anesthesia. The drug is not recommended for the treatment of PPH after vaginal delivery, thus limiting its use. CBT is administered once intravenously slowly for a minute at a dosage of 100 μg/ml [41]. Contraindications are eclampsia and preeclampsia, kidney and liver disease, epilepsy, and individual intolerance to CBT and OX.

One advantage of CBT is its resistance to environmental factors, which include the drug thermostabil, and non-requirement of cold-chain adherence for its storage and transportation [34, 42]. Temperature resistance allows its use in hot climates and in area where cold-chain storage adherence is not possible. As a result, the use of CBT in countries with similar conditions can reduce the frequency of PPH and consequently, reduce maternal mortality.

The side effects of CBT include frequent disorders of the blood system (anemia), disorders of the nervous system (headaches, dizziness, and tremor), respiratory organs (chest pain and shortness of breath), CVS (decreased blood pressure and hyperemia), digestive system (metallic taste in the mouth, nausea, vomiting, and abdominal pain), musculoskeletal system (back pain), skin, and subcutaneous tissues (itching) and general disorders of the body (feeling of heat chills and pain at the injection site).

The contraindications to the use of CBT involve the period of pregnancy and childbirth before the expected birth of the child, impairment of liver and kidney function, serious disorders of the CVS (rhythm and conduction disorders), epilepsy, and increased sensitivity to CBT and OX. The main condition when prescribing CBT should be used only for a preventive purpose and not as a reserve uterotonic. The joint use of OX and CBT may reduce the effect of the latter due to the desensitization of OURs [23, 43, 44]. In therapeutic concentrations, OX and CBT reduce the bottom and body of the uterus without having a significant effect on its lower segment, unlike other uterotonics and ergometrine that can cause a prolonged reduction of all uterus parts, including the lower segment [43].

Analysis of the effectiveness and conditions of ergometrine

Alkaloids (uterine horns and twists) are mycotoxins of the resting stage of the fungus *Claviceps purpurea* (purple spores), which parasitizes plants of the family of cereals in spring. Ergometrine and MEM are drugs belonging to uterotonics. Ergometrine is the most popular drug of this group of alkaloids with a history of more than two thousand years. MEM is a semi-synthetic analog derivative of ergometrine. These alkaloids implement their pharmacological action through the activation of alpha-adrenergic, dopaminergic, and 5HT receptors [44]. The therapeutic effect of alkaloids in intravenous administration is manifested after a minute and continues for the next 45 min, after 2–3 min in the intramuscular, and retained for the next 3 h [5]. The mechanism

of action of all natural alkaloids of ergot is attributed to their capability to increase the basal tone of the uterus. Meanwhile, large doses of alkaloids can lead to strong and prolonged contractions, contracture, and uterine tetany. The distinctive feature of the pharmacological effect of drugs in this group is their capability to cause long (within 2–3 h) normative reductions in all uterus segments. As a result, uterine contractions become intense, prompting the additional introduction of analgesics [45].

The prolonged use and overdose of ergotal alkaloids can cause ergotism and symptoms, such as high-intensity pain, gangrene limbs, ischemia of various organs and systems, and cognitive disorders due to vascular spasm. In clinical practice, repeated cases of adverse effects of alkaloids of ergot on the RSS of women giving birth have been recorded. The use of MEM is also accompanied by an increase in blood pressure, which is most pronounced in the first 24 h after birth, and the re-introduction of the drug can provoke ischemia and necrosis of the heart muscle [23, 46, 47]. One of these cases was described by scientists S. Birch and C. Lu (2019) from Taiwan, in which the patient suddenly developed atrial fibrillation against the intravenous administration of ergometrine to prevent atonal bleeding during a cesarean section [48]. Another clinical case was described in 2016, when a patient with a background of intravenous administration of a combination of MEM and OX developed acute myocardial infarction as a result of the spasm of coronary arteries [49]. Similar vasospastic effects have been described before 1990, when the use of MEM provoked a total spasm of three coronary arteries [50]. Such findings should be considered in the provision of emergency care, when clinicians often inject different combinations of UPP to save lives and stop bleeding.

The use of medicines made from alkaloid groups is associated with a high risk of complications associated with increased blood pressure, resulting from the adrenergic vasoconstrictive action, and poses a great danger to patients with CVDs, primarily those with hypertensive disorders. The use of ergometrine or MEM at a dose of 200 μg for the prevention of PPH, according to WHO recommendations, is appropriate only in the case of inefficient OX and in the absence of CVD pathology due to the high risk of hypertension in the patient. Current clinical recommendations for the prevention of PPH include limitations for the use of MEM, such as preeclampsia/eclampsia and the CVDs [41]. In addition to the pathology indicated in drug annotations, such contraindications exist for the use of ergot alkaloids, such as pregnancy, the first period of childbirth, the second period of childbirth before the birth of the fetus head, hyperthyroidism, impaired liver and kidney function, occlusion diseases of coronary and peripheral vessels, severe Raynaud's syndrome, and increased sensitivity to ergometrine [51].

With the use of drugs in this group, side effects, such as the following, may occur: tachycardia (bradycardia in several cases), nausea, vomiting, hallucinations, headache and dizziness, tinnitus, increased sweating, dyspnea, pulmonary edema, diarrhea, abdominal pain, and skin rashes [51]. A feature of the use of MEM in a distant period is the capability to reduce the secretion of the hormone prolactin, which leads to a decrease in the separation of milk in the postpartum period.

Given the possibility of causing severe reductions in the myometrium in all parts of the uterus, alkaloids are not prescribed to enhance ancestral activity. However, they can be used to prevent the emergence of PPH. According to the updated Cochrane Review (2018), the preventive use of ergot alkaloids promotes the reduction in average blood loss, increases the level of hemoglobin in the mother's blood, and reduces the need for other uterotonics. When prescribing drugs containing ergometrine, clinicians should note that that this compound is unstable in the presence of sunlight and quickly loses its activity under direct rays [51].

Analysis of the effectiveness and conditions of MSP

MSP is a synthetic analog of endogenous prostaglandin E_1; it was first synthesized in 1993 by using prostaglandins, which are a derivative of essential fatty acids synthesized from arachidonic acid in various types of cells with a wide range of activity. Natural prostaglandins are unstable in the body and have many side effects when used in medicine. Their uterotonic properties were discovered by accident, and when pregnant women were prescribed with MSP to treat peptic ulcers, they suffered from miscarriages at different stages of pregnancy. After this discovery, the analog of prostaglandin in gynecology have been used for a long time to prevent unwanted pregnancy. However, over time, the drug was proven effective against hypotonic bleeding. The pharmacological effect of MSP is implemented through specific prostaglandin receptors in the myometrium of the uterus. The medicine in interaction with the receptors EP_1 and EP_3 promotes the opening of membrane calcium channels, which entails an increase in the concentration of intracellular calcium and as a result, a reduction in the muscle fibers of the uterus [52].

To prevent hypotonic PPH, experts recommend the oral intake of MSP at a dosage of 200 or 400 μg. Its pharmacological effect develops in 9–15 min. If we consider the effectiveness of MSP in relation to PPH, according to a systematic review of domestic and international researchers, this medicine is more effective than OX [53]. However, side effects resulting from the use of MSP are pronounced, and they are associated with the polytropic effect of prostaglandins on all tissues and organs of the

female body. Differing views surround the evaluation of the effectiveness of MSP. Scientists from Pakistan (2016) did not find statistically significant differences in the comparison of the therapeutic effect of oral use of MSP and intramuscular administration of OX in the third period of childbirth [52]. A comparative study of other scientists has shown that the use of vaginal MSP is considerably greater than the effectiveness of intravenous OX in the development of PPH in women with fetal intrauterine death in the second trimester [44].

The side effects that develop with the use of MSP include nausea, vomiting, diarrhea, abdominal pain associated with reductions in myometrium, dysmenorrhea, polymenorrhea, allergic reactions, weight change, asthenia, fatigue, and extremely rare convulsions (especially in women in peri- and postmenopausal age) [5, 52]. Contraindications for the use of MSP are severe disorders of liver function, inflammatory bowel disease, pregnancy, lactation period, severe renal failure, enteritis, childhood and adolescence up to 18 years, and increased sensitivity to medicine [52].

In most countries, MSP is excluded in the registration of major medicines, despite the WHO recommendations on the use of this drug as a means of prevention in 2011 and treatment of PPH in 2015. However, the updated clinical recommendations of the Russian Federation in 2019 allowed the use of the drug in PPH based on the decision of the medical commission [43, 53]. To date, MSP in the world practice serves as an example of a medicine whose use is justified by the principles of evidence-based medicine, although it is not advertised by either manufacturers or distributors and significantly reduces the incidence of maternal mortality from PPH due to its low cost [53]. Japanese researchers Y. Yaju and co-authors (2013) believed that women who have received OX experienced no benefit from the additional use of MSP [54].

Clinicians often resort to combining several medicines to prevent the development and stop PPH. WHO experts recommend the intramuscular introduction of a combination of fixed doses of OX and ergometrine (5 IU/500 μg) in the absence of arterial hypertension. This combination can only be assigned when the isolated use of OX is not possible, or its quality is highly questionable. The meta-analysis conducted by Chinese scientists J. Tan and co-author (2016) and the comparative evaluation of the effectiveness of MSP and the combination of ergometrine and OX in the prevention of PPH involving 4,034 women with PPH. The following were observed for the group with combination of ergometrine and OX showed that the PPH level was 7.6% versus 4.2%, with relative risk (RR) of 1.81, 95% confidence interval (CI) of (1.40, 2.35) at $p < 0.01$.Meanwhile, the group in need of additional uterotonic therapy presented the following results: 19.2% compared with 10.5%; (RR) of 1.83, 95% CI, of (1.57, 2.14) at $p < 0.01$). The values were significantly higher for a group of patients receiving MSP than in the group of patients receiving ergometrine and OX [55]. However, no significant difference in the blood loss rate was observed between the groups (0.5% vs. 1.4%; RR: 0.33; 95% CI: (0.15, 0.76); $p < 0.01$). The findings have led to the conclusion that MSP is highly effective for the prevention of PPH, and its oral use is possible only in the absence of a qualified specialist (obstetrician–gynecologist) who can inject a more effective UTD [57].

All operating obstetricians and gynecologists are aware of the limited capabilities of MSP. According to the standards of the British Royal Society of Obstetricians and Gynecologists (2009), MSP is not as effective as OX, but when the OX is ineffective, MSP can be possibly applied, especially during home births [32, 33]. MSP can also lose its pharmacological activity when exposed to moisture [56, 57].

CONCLUSION

OX remains the only first-line drug for the prevention and treatment of PPH. Despite the drawbacks, such as the development of desensitization of OX with long-term infusion, instability in the environment, and loss of effectiveness in the violation of cold-chain storage conditions, OX has the best efficacy in terms of dose, duration, and pathways of introduction to myometrium at different times of pregnancy. The need for OX with predetermined therapeutic properties, minimal side effects, and optimal ways of administration and storage conditions is incredibly high, which leads to the development and search for new drugs based on synthetic analogs.

ADDITIONAL

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