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A historical narrative review through the field of tocolysis in threatened preterm birth

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ABSTRACT

Preterm birth presents a significant challenge in clinical obstetrics, requiring effective strategies to reduce associated mortality and morbidity risks. Tocolytic drugs, aimed at inhibiting uterine contractions, are a key aspect of addressing this challenge. Despite extensive research over many years, determining the most effective tocolytic agents remains a complex task, prompting better understanding of the underlying mechanisms of spontaneous preterm birth and recording meaningful outcome measures. This paper provides a comprehensive review of various obsolete and current tocolytic drug regimens that were instituted over the past century, examining both historical contexts and contemporary challenges in their development and adoption. The examination of historical debates and advancements highlights the complexity of introducing new therapies. While the search for effective tocolytics continues, questions arise regarding their actual benefits in obstetric care and the necessity for ongoing exploration. The presence of methodological limitations in current research emphasizes the importance of well-designed randomized controlled trials with robust endpoints and extended follow-up periods.In response to these complexities, the consideration of shifting towards prevention strategies aimed at addressing the root causes of preterm labor becomes more and more evident. This potential shift may offer a more effective approach than relying solely on tocolytics to delay labor initiation.Ultimately, effectively managing threatened preterm birth necessitates ongoing investigation, innovation, and a willingness to reassess strategies in pursuit of optimal outcomes for mothers, neonates, and long-term child health.

Introduction

Reducing the significant risks of mortality and morbidity associated with preterm birth has been the ongoing goal in clinical obstetrics the last century. One way of reaching this goal, is by the development of tocolytic drugs. Tocolysis, the inhibition of uterine contractions, disrupts the provoking factor in preterm birth. The premise is that by achieving uterine quiescence, the occurrence of preterm birth can be averted, thereby prolonging gestation and improving neonatal outcomes. The pursuit of effective tocolytic agents has been driven by the urgent need to address the immense burden associated with preterm birth, both in the short and long term. Preterm birth has been, and still is, the leading cause of stillbirth and neonatal mortality [1,2]. Despite efforts in recent years, researchers and clinicians have struggled to identify an optimal tocolytic drug candidate that ensures improved outcomes for preterm births. Consequently, there is a clear need for further research into the mechanisms of spontaneous preterm birth to enhance both prediction and prevention strategies. [3] This paper aims to provide both an anecdotal and comprehensive overview of the available written evidence on research into various tocolytic drug regimens.

In the historical context of the treatment of preterm birth, it is important to recognize the wide variation in medical practice and documentation across regions and over time. For example, a well-preserved correspondence between 1844–1853 among notable doctors, Sir James Y. Simpson in Scotland and London's "conservative and so curiously prejudiced" Dr. Ramsbotham, illustrates a fundamental divergence of opinion and clinical preference, even though they were

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not so far apart geographically and culturally. While Simpson advocated the use of anesthesia, including chloroform, for labor pain relief, Ramsbotham remained cautious and resistant to such innovative approaches. [4] This well-documented dispute nicely illustrates the dilemmas associated with the introduction of novel medicines. In the exploratory phase, "early adopters" begin to use novel therapies in practice, while others, more aware of the need for evidence of safety and efficacy, will be reluctant to experiment until the therapy is proven effective. While there may not be a clear-cut "first use" of specific medications for preterm birth, this paper will present a scrutinized overview of the discovery and introduction of novel agents in the treatment of threatened preterm birth. By broadening our understanding of the treatment options that have already been explored, we can better position ourselves to develop potential therapies for the future.

Childbirth: from ancient beginnings to the start of a modern approach

For centuries, possibly millennia, humans have strived to aid the weak and cure the ill, with signs of cranial surgery tracing back to 5000 B.C. [5] The earliest traces of medicine concerning pregnancy and childbirth, are prehistoric figures and ancient Egyptian drawings picturing women giving birth, usually with her (grand)mothers, other female relatives or gods as accompanying attendants. .

First steps towards medical treatment of preterm birth

Although "adequate rest", "a nourishing diet", possibly enriched with some morphine were long posed as the mainstay in treating women with preterm contractions, serious steps in the field of complications of pregnancy, especially spontaneous miscarriage and preterm birth, were not taken until the 20th century. [1,6] The first attempts to control preterm birth date back to the 1930 s, with initial strategies focused on a mysterious substance that could return fertility in sterile animals. [7] When replicated on a larger scale, the serendipitous finding of improved pregnancy outcomes in animals, that disappeared in individuals who were inadvertently not treated properly, led to the hypothesis that preterm birth might be due to a chemical imbalance that, if corrected, could prevent this serious condition. [8] In the subsequent decades, researchers delved into various drugs, each era bringing new insights and better understanding of the molecular pathways. The hope was to discover a more effective treatment, allowing clinicians to finally put an end to preterm birth without compromising the well-being of both mother and baby.

Fig. 1. Woman giving birth in squatting position, with Hathor, the goddess of childbirth on her side. Ptolemaic period, now in Tahrir, Egypt.

Vitamin E

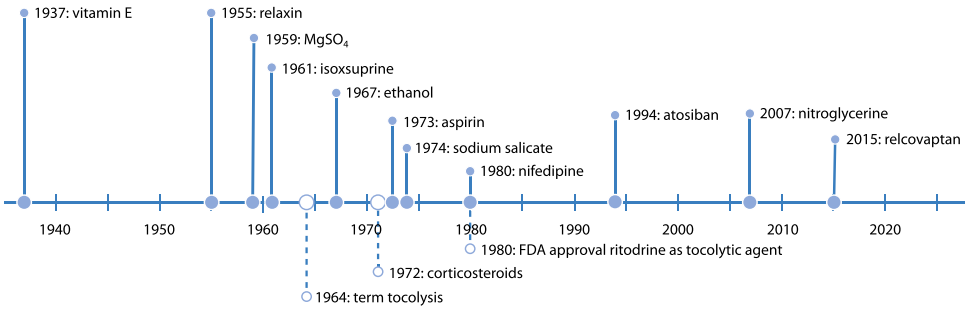
Californian anatomists and physiologists Herbert Evans and Katharine Scott Bishop, discovered vitamin E in fresh green leaves of lettuce in 1922. They found this substance, which they initially called "substance X", could restore fertility in mice that were proven to be sterile. [7] This experiment was replicated in cows by the Danish veterinarian Vogt--Müller, who in 1931 treated cows with an intramuscular formulation of wheat germ oil, known to contain a high concentration of vitamin E. [9] Some of his study subjects were delivered prematurely even while receiving doses of a vitamin E. However, on further scrutinization, it was found that the doses were not administered properly, had become rancid, or were stored at too high temperature. [8] This inspired the Canadian obstetrician Evan Shute to formulate a common biochemical explanation for miscarriage and preterm birth, and proposed a potential treatment with vitamin E. His comprehensive paper describing biochemical, endocrinological and clinical aspects of vitamin E and many other homeostatic components involved with the (patho)physiological course of pregnancy was published in the Journal of Obstetrics and Gynaecology of the British Empire, the current *BJOG*. Shute notes that a newly discovered estrogenic substance, chemically closely related to estrin (a precursor of estrogen and demonstrated inducer of iatrogenic abortion), exhibits an equilibrium with vitamin E. He demonstrated that if this balance is disturbed, miscarriage or premature labor may occur, and when the depleted compound is administered, contraction would cease. [8] Much later the exact mechanism was better understood: estrogens elevate the resting potential of muscle cells by augmenting intracellular potassium levels but also raise the concentrations of phosphocreatine, actin, and myosin. Furthermore, they enhance the activity of ATPase, consequently increasing the transmission speed of stimuli. By elevating estrogen levels during the final trimester, the myometrium undergoes preparation for the active labor process while concurrently safeguarding against symptomatic and unwanted contractions. [10] With this article, Evan Shute started the quest for an effective and safe treatment to treat preterm contractions in 1937..

Relaxin

The next breakthrough in the field of treating preterm contractions occurred in 1955, when relaxin, a hormone previously discovered by Frederick Hisaw in 1926 in his research after pubic symphysis relaxation in pregnant guinea pigs, was first applied to pregnant women. [11] Abramson and Reid, two obstetricians at Harvard Medical School, described in a case series of five patients who were admitted between 29 and 31 weeks' gestation, a therapy with a 100% success rate using the commercially prepared corpus luteum hormone relaxin. [12] The mechanism of action of relaxin is thought to involve inhibition of the stimulatory effect of prostaglandin F2-alpha. In addition, relaxin does not inhibit prostaglandin release after incubation with arachidonic acid. This suggests that relaxin may inhibit phospholipase A2, the enzyme responsible for producing arachidonic acid, a crucial precursor in prostaglandin synthesis. [13] In the decades that followed, various attempts were made to incorporate relaxin as a clinically useful tocolytic agent, which were halted in 2013 by a Cochrane review that concluded that there was insufficient evidence to support its use in clinical practice. [14].

Opiates

Amidst the promotion of various new treatment modalities, it's important to acknowledge that alongside successes, also valuable negative findings were reported. Over the years, morphine, being a relaxant for the mind, has been used to "furnish the patient with genuine



1937 Vitamin E as first medicine to inhibit preterm contractions
1955 Relaxin
1959 MgSO4
1961 Beta-mimetics: isoxsuprine
1964 Term 'tocolysis' appears in literature
1967 Ethanol
1972 Corticosteroids for lung maturation
1973 Aspirin
1974 Prostaglandin synthesis inhibitors: sodium salicylate
1980 Calcium channel blockers: nifedipine
1980 FDA approval of first tocolytic agent: ritodrine
1994 Oxytocin receptor antagonists: atosiban
2007 Nitric oxide donors: nitroglycerine
2015 Arginine-vasopressin-receptor antagonists: relvocaptan

Fig. 2. Introduction of tocolytic medications, grouped by category or presented individually if of specific interest.

obstetric rest". Morphine, an opium alkaloid derived from the seed capsule of the poppy plant, possesses potent analgesic and sedative properties. In need for a scientific verdict, AJOG published a trial by the Dutch gynecologist Tom Eskes in 1962, which put an end to the myth that morphine could effectively cease uterine contractions. [15] Recently, a 2024 case-control study involving 25,391 women concluded that opioid usage in the two months preceding the due date leads to an increased incidence of preterm birth. The authors found an association between the administered opioid dose and the likelihood of spontaneous preterm birth. [16].

Ethanol

With one potential treatment modality lost, no major steps were taken until 1963, when the endocrinologist Anna-Riitta Fuchs published a series of articles about the tocolytic effect of ethanol in rabbits, and later in humans. [17–19] Ethanol has its tocolytic effect at high concentrations, by acting as an inhibitor of oxytocin and vasopressin release from the posterior pituitary gland. [20] In the 1967 one-armed trial with 68 patients, that she conducted with her husband Fritz, an inhibitory effect on uterine contractions was observed. [21] A salient detail is that Fuchs herself chose to undergo intravenous ethanol therapy during the pregnancy of her last child. After the preterm contractions ceased, she carried her son Lars until full term two months later. [22] Over a span of 20 years, the couple kept investigating the tocolytic effect of alcohol, inspiring others to explore this topic as well. [23] In 2015, a Cochrane review, encompassing all available evidence, including studies dating back to 1987, advised against the use of ethanol use in clinical practice due to safety concerns for both the mother and her baby. They noted that long-term follow-up on the babies would be useful to assess the long--term neurodevelopmental status. [24] Unfortunately, even Fuchs did not publish her scientific findings about her son. In total, twelve trials who had registered the data of 1586 women were carried out. Only one of them was found to be of good quality by the CONSORT criteria, and this study concluded no significant difference between ethanol and conventional treatment. [25] Given ethanol's dubious reputation as a tocolytic drug and concerns about safety, ethanol was completely abolished from the list of potential effective drug treatments for preterm birth.

Magnesium sulphate

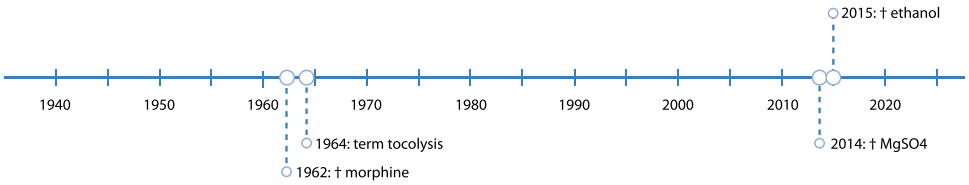
In 1924, Dr. Bogen, a medical resident in the Los Angeles General Hospital, hypothesized that magnesium sulphate ($MgSO_4$) could be used for the control of eclamptic convulsions. Having in mind the sedative action of magnesium sulphate on the nerve cells, as well as the intraspinal use of magnesium sulphate for the control of tetanic convulsions, a trial with 575 patients was conducted, demonstrating impressive control of eclamptic attacks. [26,27] Magnesium sulphate reduces the frequency of smooth muscle depolarization by modulating calcium uptake, binding, and distribution within smooth muscle cells. [28] In 1959, the American Obstetrician David Hall, tested the clinical observation that magnesium sulphate, also results in a prolongation of gestation, which was found to be the case with a dose-related effect in a study of 300 patients with toxic eclampsia. [29] Following numerous prior publications, a Cochrane review in 2014 brought an end to the practice of using magnesium sulphate to delay preterm birth. The review concluded that $MgSO_4$ is ineffective in delaying preterm birth. [28] The anticonvulsive and neuroprotective effects in eclampsia and very preterm infants were recognized, and thus, $MgSO_4$ kept its therapeutic role in preterm birth, however not as tocolytic treatment. [30].

Current tocolytics

The foundation for tocolytic drugs still in use today was already laid over 70 years ago. With the introduction of beta-adrenergic agonists, a new era of research dawned. In this period, also research evolved to a much more formal field of study, this was reflected in the study designs and articles published..

Beta-adrenergic agonists (Beta-mimetics)

Beta-adrenergic receptors are G protein-coupled receptors, and are coupled to the enzyme adenylate cyclase. Binding to this receptor, results in generation of intracellular cyclic adenosine monophosphate (cAMP). This in turn affects myometrial cells by inhibiting myosin light-chain kinase through direct phosphorylation. A secondary effect is the reduction of intracellular calcium levels. These two mechanisms both lead to smooth muscle relaxation. In the USA in 1960, isoxsuprine was found to relax the myometrium in rabbits, cats and dogs in varying stages of pregnancy. [32] In 1961, it was successfully used in humans. [33,34] A multicenter series of placebo-controlled clinical trials that



1962 Morphine use in preterm contractions discredited by Dutch gynecologist Tom Eskes
1964 Term 'tocolysis' appears in literature
1980 Calcium channel blockers: nifedipine
2014 Cochrane review ends the recommendation of magnesium sulphate as a tocolytic. It keep a place as fetal neuroprotector
2015 Cochrane review ends the recommendation of ethanol as a tocolytic

Fig. 3. The various intracellular targets to inhibit the contraction of the uterine myocyte.
Adapted from: R Smith, NEJM 2007. [31].

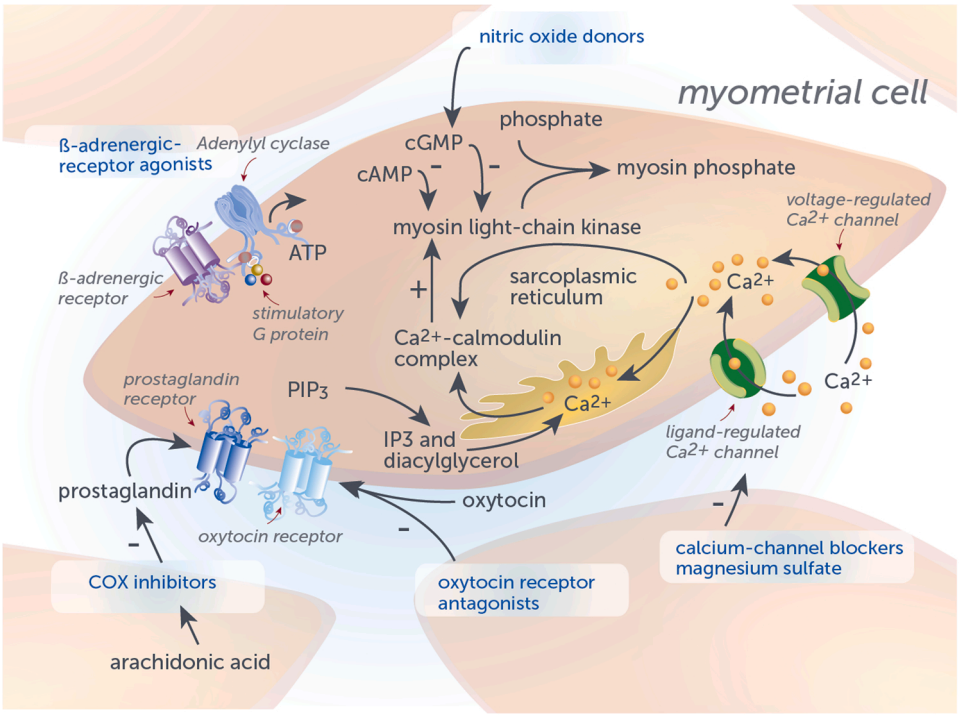


Fig. 4. skeletal structure of ritodrine.

started in 1972 investigated ritodrine and included 366 pregnant women in 5 years. 61% of the patients received ritodrine, 21% received intravenous ethanol, and 18% were administered an intravenous placebo. The authors found a lower incidence of neonatal death as well as favorable other neonatal outcomes in the ritodrine group. Although by today's standards this study did not generate very sturdy results, the FDA used these finding to list ritodrine as the first approved tocolytic agent ever. [35,36] Fenoterol, another commonly used tocolytic, was discovered to provide comparable efficacy and side effect profiles, solidifying the place of beta-mimetics in tocolytic practice. [37] Ritodrine was the most widely used tocolytic in the 1990 s and 2000 s [38] Although effective in delaying birth for 48 h, adverse events including chest pain, dyspnea, palpitations, headache, hyperglycemia are over 10 times more common than with placebo. [39,40] Even though delaying birth for 48 h is sufficient for administering an antenatal course of corticosteroids, this has not resulted in measurable improvements in neonatal outcomes. [39] Given this adverse effect profile, betamimetic use around the world decreased rapidly in the last decade, but even in the 2020 s, isoxsuprine, the first beta-mimetic used in threatened preterm birth, remained in use in some settings. [41].

Prostaglandin synthesis inhibitors (NSAIDs / COX inhibitors / PSIs)

Prostaglandins, a group of hormones with diverse functions, play a crucial role in initiating uterine contractions during labor. Among many other effects, prostaglandins influence myometrial contraction by increasing intracellular calcium levels and activating myosin light chain kinase. [42] Nonsteroidal anti-inflammatory drugs (NSAIDs) act as cyclo-oxygenase inhibitors (COX inhibitors). By inhibiting COX, these medications, also known as prostaglandin synthesis inhibitors (PSIs), prevent the production of prostaglandins.

The English physiologist Vernon Pickles first published his findings on prostaglandins and their relation to smooth muscle contractions in Nature by the end of 1957. [43] He discovered that a lipid-soluble acidic substance could be isolated from menstruation dressings from healthy medical students. When reapplied to a rat uterus, increased muscle tone and contractions were observed. This discovery led, through a number of intermediate steps, to a hypothesis posed by American physician Richard Lewis. He thought that if this substance, now identified as prostaglandin, could cause uterine contractions, its inhibition could prolong pregnancy.

In 1973, Lewis conducted a retrospective study together with Joseph Schulman, who became later a pioneer in the field of in vitro fertilization

(IVF). [44] They analyzed a 20-year retrospective cohort of 103 patients who received at least 3250 mg of aspirin daily (mainly for rheumatoid arthritis) for at least the last 6 months of pregnancy. The action of aspirin is attributed to altering the pathophysiological mechanism responsible for uteroplacental ischemia through its effect on the COX receptors, employing a similar approach to that which has been effective in treating preeclampsia. [45] Despite no significant decrease in preterm deliveries, the study found a 70% longer delivery time and a significantly higher percentage of infants born after 42 weeks. Apart from mentioning birth weights, no word was written about neonatal status, especially on now well-known adverse events such as oligohydramnios, kidney problems, premature closure of the ductus arteriosus, necrotizing enterocolitis and intraventricular hemorrhage. [46].

While the results of this study did not directly indicate added value in the treatment of preterm birth, they did lay the groundwork for the use of PSIs as tocolytics. PSIs garnered significant research attention following a prospective study by the Hungarian obstetrician Dr. György on sodium salicylate in 1974. In 50 women, he found that the medication diminished uterine activity, although no details were described. A few months later, a group led by Henryk Zuckerman published the first full article describing the use of indomethacin. [47,48] Following the discovery of the first PSIs, a myriad of different prostaglandin-lowering agents was marketed, including rheopyrin, flufenamic acid, sulindac, diclofenac, ibuprofen, naproxen and indomethacin.

Indomethacin, despite being a nonselective COX inhibitor with the potential for more side effects, is currently the most widely used PSI for tocolysis in the United States. This is primarily due to its effectiveness in delaying delivery. [40,49,50] However, a comprehensive Cochrane meta-analysis, which also assessed the quality of evidence, found no clear benefit in neonatal outcomes for COX inhibitors over placebo. Additionally, there was no indication of a better adverse effects profile in selective COX inhibitors, such as celecoxib. [46].

Calcium channel blockers

Calcium channel blockers were originally intended for the treatment of hypertension. It also acts on myometrial cells. Calcium channel blockers exert their pharmacological action downstream in the signaling cascade by blocking voltage-regulated calcium channels. The channels open when an activating ligand (e.g., prostaglandin or oxytocin) reduces the electrochemical gradient across the myocyte membrane. These ligand-regulated channels, which release calcium from intracellular stores, are activated by prostaglandins and oxytocin. This ultimately promotes myocyte contraction. [31] In 1978, the Swedish obstetrician Ulf Ulmsten conducted preparatory investigations of the calcium channel blocker nifedipine using in vitro, animal, and non-pregnant uteri. Through these studies, he discovered the inhibitory effect of nifedipine on uterine activity, resulting in decreased myometrial contractions and basal tone. [51,52] Two years later, he demonstrated the efficacy of the calcium channel blocker nifedipine as a tocolytic agent in a pilot observational study. He included 10 primigravidae with intact membranes and a cervical dilatation under 5 centimeters during a pregnancy between 28 and 33 weeks. [53] In his article, he remarkably used the term “carefully selected” to describe that out of 3000 women who delivered during the one-year inclusion period, only 10 contributed to the conclusion that nifedipine is effective and safe in postponing delivery. A sheep study showed that nifedipine may have adverse effects on fetal and placental circulation. [54] Indeed, one human case report has been published describing severe hypotension followed by fetal death after restarting tocolysis with nifedipine. However, in subsequent studies, no evidence of inadequate blood flow to the fetus could be demonstrated. It is debated whether this undermines the extensive evidence supporting the safety of nifedipine as a tocolytic agent. [55,56] Nifedipine was slow to be adopted by clinicians, as reflected by the fact that the first placebo-controlled trial comparing nifedipine with ritodrine in 40 patients was not conducted until 1986. [57] After this, in many trials the effectiveness of nifedipine was confirmed to be at least comparable to ritodrine. [58] Due to its high efficacy in treating hypertension, and no variant selective to the myometrium was discovered, most maternal side-effects are related to the effect on the blood pressure. These include hypotension, headache, flushing, nausea, tachycardia and vomiting. However, compared to beta-mimetics, the occurrence of both maternal and fetal side effects is modest and less frequent. [59,60] Assuming that maternal hypotension precedes any adverse fetal effects, it seems plausible that protocol monitoring of maternal blood pressure is sufficient to assure drug safety, but there may be other mechanisms that influence neonatal outcome. In this context, the APOSTEL 3 trial raised concerns about the safety of nifedipine, showing a non-significant, but twofold increase in neonatal mortality compared with atosiban. Nicardipine, which can be administered both orally and intravenously has been proposed as potential successor to nifedipine. [61] Until today, nifedipine is widely used in clinical practice as first-choice tocolytic to allow enough time for antenatal corticosteroids to have their effect. [62] .

Oxytocin receptor antagonists (OTR antagonists)

Oxytocin receptor antagonists act by competition with oxytocin at its receptors on the myometrial plasma membrane, inhibiting the second messenger process that normally leads to an increase in intra-cellular free calcium. Atosiban is a synthetic peptide oxytocin antagonist that resembles oxytocin, but has modifications at the 1, 2, 4, and 8 positions of the molecule. It binds to the oxytocin (and vasopressin) receptor, mimicking oxytocin, but because of the modifications it blocks signaling further down the pathway. This ultimately prevents release of calcium from the sarcoplasmic reticulum, subsequent opening of voltage-gated calcium channels, and eventual contraction of the myometrial cells. [63].

In 1994, after in-vitro and animal experiments, atosiban was investigated in a placebo-controlled trial including 120 women from 20 to 36 weeks’ gestation with contractions and less than 3 cm dilatation. [64] A greater decline in contraction frequency was noted in patients receiving atosiban compared with controls. No significant adverse events were recorded. This paved the way for other trials, most notably an RCT by Romero and colleagues in 2000. [65] They included 501 women with a gestational age between 20 and 34 weeks who experienced preterm labor with intact membranes. This group was 1:1 randomized to receive either atosiban or placebo, with standard care including the administration of another tocolytic if needed after one hour. In almost half of the subjects, rescue therapy with another tocolytic drug was given. In the total study population, time to delivery was not different. In women admitted at a gestational age of less than 26 weeks, 10 out of 27 children died, compared to 0 out of 16 in the placebo group. However, it was found that in the post-hoc defined subgroup of gestational age $\geq$ 28 weeks, there was a longer prolongation of pregnancy in the atosiban group without a higher adverse events rate. In the following years, several studies have been conducted on atosiban. However, the Cochrane review on oxytocin receptor antagonists failed to demonstrate the superiority of atosiban over calcium channel blockers, beta-adrenoceptor agonists or placebo. [66] In the last years, the APOSTEL 8 trial has been performed in the Netherlands, a placebo-controlled trial investigating the effectiveness of atosiban in

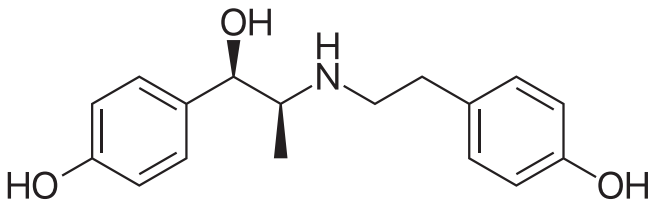


Fig. 5. skeletal structure of oxytocin, arginine vasopressin, and atosiban. [73].

women with threatened preterm birth, the results are to be expected in 2025. [67] Furthermore, there is no indication that atosiban, like nifedipine, may have direct neuroprotective effects. [68] Alongside atosiban, the group of OTR antagonists encompasses barusiban, characterized by its high selectivity for the oxytocin receptor (OTR), potent activity, and subcutaneous administration as well as the orally administered retosiban and nolasiban. [69–73].

Miscellaneous attempts for a satisfactory tocolytic agent

Despite ongoing scientific efforts to discover a tocolytic capable of mitigating the adverse effects of preterm birth and minimizing risks of medication use to both mother and child, numerous trials have failed to identify an ideal candidate drug that significantly improves neonatal outcomes. In this quest, two additional potential drug groups have been proposed in the 21st century.

Arginine-vasopressin-receptor antagonists

Relcovaptan, a medicine that acts on the arginine-vasopressin-receptor, and can be used to treat Raynaud's phenomenon, was found to also have an agonist affinity on the oxytocin receptor. [74] Initially, it was investigated for to cease uterine contractions in non-pregnant women suffering from dysmenorrhea. [75] In 2005, the same researcher used relcovaptan in a RCT by on pregnant women with threatened preterm birth. [76] 12 women received the medication and 6 patients received placebo. In this small Phase I study group, a statistically significant effect favoring relcovaptan in resolving uterine contractility was observed. Nevertheless, no neonatal outcomes were recorded, no subsequent publications followed, and no trials were registered to further investigate this drug..

Nitric oxide donors

Relatively recently, a very favorable candidate to fulfil the promise of the ideal tocolytic agent was introduced in clinical practice: nitroglycerine.

The use of the chemical substance glyceryl trinitrate (GTN), also known as nitroglycerine, dates back to 1847 when the Italian physician-chemist Ascanio Sobrero found out about its explosive capacities. The substance proved to be nearly impossible to apply safely in practice. One of the other students at the faculty, Alfred Nobel, in the 1860's refined and mixed the substance, with this discovering dynamite. In this era of roaring scientific discoveries, medical doctors did not hesitate to administer novel substances to their patients. In 1879, British physician William Murrell published a case series of 35 patients apparently suffering from angina pectoris, although neither the characteristics nor the effect of the drugs administered on the angina symptoms were described outside the title. Still in this article, he was the first one to

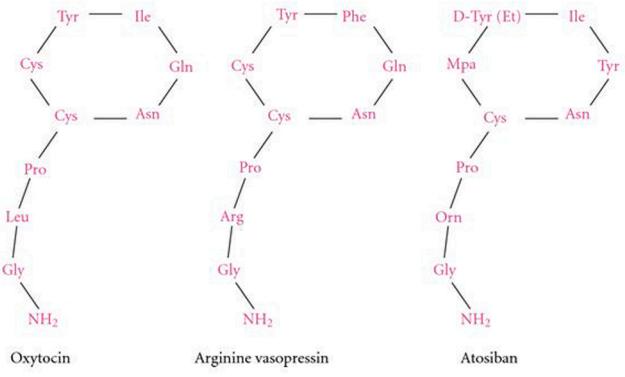


Fig. 6. skeletal structure of nitroglycerin.

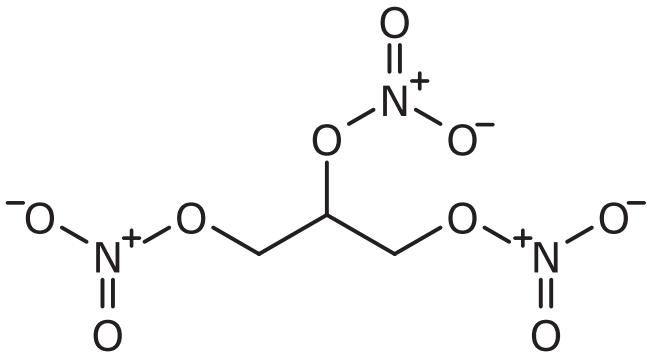


Fig. 7. discontinued and/or discredited medicine groups used for tocolysis.

describe the medical use of nitroglycerine, evidently leading to side effects such as severe headache and palpitations. [77].

Over a century later, as recent as in 1999, the Canadian obstetrician Dr Smith investigated nitroglycerine as an experimental treatment modality in women with preterm contractions. [78].

Nitroglycerin is metabolized to nitric oxide (NO) within the body. This process activates a pathway wherein guanosine monophosphate (GMP) is converted to guanosine triphosphate (GTP). [79,80] Additionally, nitric oxide itself plays a role in the activity of potassium channels and facilitates the conversion of prostaglandin E2 to prostaglandin F2-alpha. [81] These processes ultimately lead to relaxation of smooth muscle cells, thereby diminishing uterine contractions.

In their pilot study, Smith *et al.* found that 35% of the mothers delivered within 48 h in the treatment group, compared with 63% in the placebo group. No significant fetal or maternal side effects were found. This study was followed up by the same Dr Graeme Smith in a full-sized RCT published in 2007. He randomized 153 women between 24 and 32 weeks and the primary outcome was changed from delay of delivery to a composite fetal outcome. This occurred less often in the treatment group. However, many women suffered from side effects of the transdermal nitroglycerine patch. [80] Since then, a systematic review by Roberto Romero and colleague reported that the current evidence does not support its use as tocolytic agent for the treatment of preterm labor, also because it is associated with significant maternal side effects, a position that was confirmed by a Cochrane review and the ACOG guideline. [82–84].

Future of tocolysis

Would this close the circle for tocolysis in Canada, almost 80 years after Evan Shute was the first physician to systematically assess the tocolytic capacities of vitamin E?

The efficacy and role of tocolytics in managing threatened preterm birth remain subjects of ongoing research. Despite the extensive research conducted, many studies suffer from methodological flaws, including inadequate design and a lack of placebo-controlled trials.

As we reflect on the collective efforts invested in exploring tocolytic therapies, the fundamental question persists: what have tocolytics truly brought to obstetric care? As we consider the efforts invested in researching tocolytic therapies, the core question persists: what tangible benefits have tocolytics truly brought to obstetric care until now? Are we approaching our exploration effectively and should our pursuit continue? If so, in what direction should our efforts be directed?

The quest for answers drives us to advocate for well-conducted randomized controlled trials, integrating robust endpoints and meaningful neonatal outcomes, along with long-term follow-up. However, in the midst of our pursuit, we're left wondering if it might be time for a shift in approach. Could prevention strategies, targeting preterm labor's underlying causes before its onset, offer a more effective approach than solely relying on tocolytics to delay labor once initiated? As we navigate

these questions, the path forward in managing threatened preterm birth requires not only continued investigation but also a willingness to reassess and innovate in pursuit of optimal maternal and neonatal outcomes.

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Tijn van Winden: Conceptualization, Data curation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Martijn A. Oudijk:** Supervision, Writing – review & editing. **Carolien Roos:** Supervision, Writing – review & editing. **Eva Pajkrt:** Conceptualization, Writing – review & editing. **Ben W. Mol:** Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest.

References

[1] Shute E. Vitamin E in habitual abortion and habitual miscarriage. BJOG 1942 Oct; 49(5):534–41.
[2] Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10 (Suppl 1):S2. Suppl 1.
[3] Vogel JP, Chawanpaiboon S, Moller A-B, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. Best Pr Res Clin Obstet Gynaecol 2018 Oct;52:3–12.
[4] Waserman M. Sir James Y Simpson and London's "conservative and so curiously prejudiced" Dr Ramsbotham. BMJ 1980 Jan 19;280(6208):158–61.
[5] Alt KW, Jeunesse C, Buitrago-Téllez CH, Wächter R, Boës E, Pichler SL. Evidence for stone age cranial surgery. Nature 1997 May 22;387(6631). 360–360.
[6] Snyder FF. Obstetric Analgesia and Anesthesia, Their Effects Upon Labor and the Child. Anesth Analg 1949 Jan;28(1):268.
[7] Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. 1979 Science 1922 Dec 8;56(1458):650–1.
[8] Shute E. Anti-proteolytic properties of human blood-serum in cases of miscarriage and premature Labour. BJOG 1937 Apr;44(2):253–63.
[9] Vogt-Moller P, Bay F. On treatment of sterility in cows with wheat germ oil (Vitamin E) (1900) Vet J 1931 Apr;87(4):165–70.
[10] Koutras A, Fasoulakis Z, Syllaios A, Garmpis N, Diakosavvas M, Pagkalos A, et al. Physiology and pathology of contractility of the myometrium. Vivo 2021;35(3): 1401–8.
[11] Hisaw F.L. Experimental relaxation of the pubic ligament of the guinea pig. In: Proceedings of the Society for Experimental Biology and Medicine. SAGE Publications Sage UK: London, England; p. 661–663.
[12] Abramson D, Reid DE. Use of relaxin in treatment of threatened premature labor. J Clin Endocrinol Metab 1955 Feb;15(2):206–9.
[13] Weiss G. Relaxin. Annu Rev Physiol 1984 Oct;46(1):43–52.
[14] Bain E, Heatley E, Hsu K, Crowther CA. Relaxin for preventing preterm birth. Cochrane Database Syst Rev 2013 Aug 16.
[15] Eskes TKAB. Effect of morphine upon uterine contractility in late pregnancy. Am J Obstet Gynecol 1962 Aug;84(3):281–9.
[16] Bosworth OM, Padilla-Azain MC, Adgent MA, Spieker AJ, Wiese AD, Pham A, et al. Prescription opioid exposure during pregnancy and risk of spontaneous preterm delivery. JAMA Netw Open 2024 Feb 14;7(2):e2355990.
[17] Fuchs A-R, Wagner G. Effect of alcohol on release of oxytocin. Nature 1963 Apr; 198(4875):92–4.
[18] Fuchs A-R, Wagner G. The effect of ethyl alcohol on the release of oxytocin in rabbits. Acta Endocrinol (Copenh) 1963 Dec;44(4):593–605.
[19] Fuchs A-R. The inhibitory effect of ethanol on the release of oxytocin during parturition in the rabbit. J Endocrinol 1966 Jun;35(2):125–34.
[20] Schaefer C., Peters PWJ, Miller R.K. Drugs During Pregnancy and Lactation. 2nd edition. Elsevier;
[21] Fuchs F, Fuchs A-R, Poblete VF, Risk A. Effect of alcohol on threatened premature labor. Am J Obstet Gynecol 1967 Nov;99(5):627–37.
[22] The New York Times - Anna-Riitta Fuchs. [https://www.legacy.com/us/obituaries/nytimes/name/anna-riitta-fuchs-obituary?id=23435515]. Accessed 2022 May 14.
[23] Zervoudakis IA, Krauss A, Fuchs F. Infants of mothers treated with ethanol for premature labor. Am J Obstet Gynecol 1980 Jul 15;137(6):713–8.
[24] Haas DM, Morgan AM, Deans SJ, Schubert FP. Ethanol for preventing preterm birth in threatened preterm labor. Cochrane Database Syst Rev 2015 Nov 5;2015(11).
[25] Watring WG, Benson WL, Wiebe RA, Vaughn DL. Intravenous alcohol – a single blind study in the prevention of premature delivery: a preliminary report. J Reprod Med 1976 Jan;16(1):35–8.
[26] Lazard EM. A preliminary report on the intravenous use of magnesium sulphate in puerperal eclampsia. Am J Obstet Gynecol 1924 Oct.
[27] Lazard EM. An analysis of 575 cases of eclamptic and pre-eclamptic toxemias treated by intravenous injections of magnesium sulphate. Am J Obstet Gynecol 1933;26(5):647–56.
[28] Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2014 Aug 15;2014(8).
[29] Hall DG, McGaughey HS, Corey EL, Thornton WN. The effects of magnesium therapy on the duration of labor. Am J Obstet Gynecol 1959 Jul;78(1):27–32.
[30] Crowther CA, Middleton PF, Voysey M, Askie L, Duley L, Pryde PG, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. PLoS Med 2017 Oct;14(10):e1002398.
[31] Smith R. Parturition. N Engl J Med 2007 Jan 18;356(3):271–83.
[32] Lish PM, Hillyard IW, Dungan KW. The uterine relaxant properties of isoxsuprine. J Pharm Exp Ther 1960 Aug;129:438–44.
[33] Bishop E, Woutersz T. Isoxsuprine, a myometrial relaxant: a preliminary report. Am J Obstet Gynecol 1961;17:442–6.
[34] Hendricks CH, Cibils LA, Pose SV, Eskes TKAB. The pharmacologic control of excessive uterine activity with isoxsuprine. Am J Obstet Gynecol 1961 Nov;82: 1064–78.
[35] Barden TP, Peter JB, Merkatz IR. Ritodrine hydrochloride: a betamimetic agent for use in preterm labor. I. pharmacology, clinical history, administration, side effects, and safety. Obstet Gynecol 1980 Jul;56(1):1–6.
[36] Merkatz IR, Peter JB, Barden TP. Ritodrine hydrochloride: a betamimetic agent for use in preterm labor. II. Evidence of efficacy. Obstet Gynecol 1980 Jul;56(1):7–12.
[37] Essed GGM, Eskes TKAB, Jongsma HW. A randomized trial of two beta-mimetic drugs for the treatment of threatening early labor. Eur J Obstet Gynecol Reprod Biol 1978 Dec;8(6):341–8.
[38] Papatsonis DN, Van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol 1997 Aug;90(2):230–4.
[39] Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev 2014;2014(2).
[40] Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012 Oct 9;345(oct09 2). e6226–e6226.
[41] Haas D, Benjamin T, Sawyer R, Quinney S. Short-term tocolytics for preterm delivery – current perspectives. Int J Women's Health 2014 Mar:343.
[42] Qureshi O., Dua A. COX Inhibitors.
[43] Pickles VR. A plain-muscle stimulant in the menstruum. Nature 1957 Nov;180 (4596):1198–9.
[44] Lewis RichardB, Schulman JosephD. Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labour. Lancet 1973 Nov;302(7839):1159–61.
[45] Landman AJEMC, de Boer MA, Visser L, Nijman TAJ, Hemels MAC, Naaktgeboren CN, et al. Evaluation of low-dose aspirin in the prevention of recurrent spontaneous preterm labour (the APRIL study): A multicentre, randomised, double-blinded, placebo-controlled trial. PLoS Med 2022 Feb;19(2): e1003892.
[46] Reinebrant HE, Pileggi-Castro C, Romero CLT, dos Santos RAN, Kumar S, Souza JP, et al. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database Syst Rev 2015 Jun 5;2015(6).
[47] Györy G, Kiss C, Benyó T, Bagdány S, Szalay J, Kurcz M, et al. Inhibition of labour by prostaglandin antagonists in impending abortion and preterm and term labour. Lancet 1974 Aug;304(7875):293.
[48] Zuckerman H, Reiss U, Rubinstein I. Inhibition of human premature labor by indomethacin. Obstet Gynecol 1974 Dec;44(6):787–92.
[49] Abramovici A, Cantu J, Jenkins SM. Tocolytic therapy for acute preterm labor. Obstet Gynecol Clin North Am 2012 Mar;39(1):77–87.
[50] Elpek G, Uner M, Trak B, Akinci Z, Zorlu CG. Intravaginal naproxen in preterm labour: a preliminary study. J Obstet Gynaecol 1998 May;18(3):236–7.
[51] Sandahl B, Andersson KE, Aronsen KF, Ulmsten U. Effect of the calcium antagonist nifedipine on uterine blood flow in non-treated and oestradiol-treated rats. Gynecol Obstet Invest 1978;9(5):238–43.
[52] Ulmsten U, Andersson KE, Forman A. Relaxing effects of Nifedipine on the nonpregnant human uterus in vitro and in vivo. Obstet Gynecol 1978 Oct;52(4): 436–41.
[53] Ulmsten U, Andersson KE, Wingerup L. Treatment of premature labor with the calcium antagonist nifedipine. Arch Gynecol 1980 Jan;229(1):1–5.
[54] Harake B, Gilbert RD, Ashwal S, Power GG. Nifedipine: effects on fetal and maternal hemodynamics in pregnant sheep. Am J Obstet Gynecol 1987 Oct;157(4 Pt 1):1003–8.
[55] Pirhonen JP, Erkkola RU, Ekblad UU, Nyman L. Single dose of nifedipine in normotensive pregnancy: Nifedipine concentrations hemodynamic responses, and uterine and fetal flow velocity waveforms. Obstet Gynecol 1990;76(5 I):807–11.
[56] Mari G, Kirshon B, Moise KJ, Lee W, Cotton DB. Doppler assessment of the fetal and uteroplacental circulation during nifedipine therapy for preterm labor. Am J Obstet Gynecol 1989;161(6 PART 1):1514–8.
[57] Read MD, Wellby DE. The use of a calcium antagonist (nifedipine) to suppress preterm labour. Br J Obstet Gynaecol 1986 Sep;93(9):933–7.

[58] Van De Water M, Kessel ET-V, Van, De Kleine MJ, Oei SG. Tocolytic effectiveness of nifedipine versus ritodrine and follow-up of newborns: a randomised controlled trial. Acta Obstet Gynecol Scand 2008;87(3):340–5.
[59] Papatsonis DNM, van Geijn HP, Bleker OP, Adèr HJ, Dekker GA. Hemodynamic and metabolic effects after nifedipine and ritodrine tocolysis. Int J Gynaecol Obstet 2003 Jul;82(1):5–10.
[60] Flenady V., Wojcieszek A.M., Papatsonis D.N., Stock O.M., Murray L., Jardine L.A., et al. Calcium channel blockers for inhibiting preterm labour and birth. In: Flenady V, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; p. CD002255.
[61] McDougall ARA, Hastie R, Goldstein M, Tuttle A, Ammerdorffer A, Gülmezoglu AM, et al. New medicines for spontaneous preterm birth prevention and preterm labour management: landscape analysis of the medicine development pipeline. BMC Pregnancy Childbirth 2023 Jul 18;23(1):525.
[62] National Institute for Health and Care Excellence. NICE guideline Preterm labour and birth. 2015 Nov;(November 2015).
[63] Drugbank online: Atosiban. [https://go.drugbank.com/drugs/DB09059]. Accessed 2023 Apr 24.
[64] Goodwin TM, Paul R, Silver H, Spellacy W, Parsons M, Chez R, et al. The effect of the oxytocin antagonist atosiban on preterm uterine activity in the human. Am J Obstet Gynecol 1994 Feb;170(2):474–8.
[65] Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille J-C, Tabor B, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: A randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol 2000 May 1;182(5):1173–83.
[66] Flenady V., Reinebrant H.E., Liley H.G., Tambimuttu E.G., Papatsonis D.N.M. Oxytocin receptor antagonists for inhibiting preterm labour. In: Flenady V, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; p. CD004452.
[67] Klumper J, Breebaart W, Roos C, Naaktgeboren CA, van der Post J, Bosmans J, et al. Study protocol for a randomised trial for atosiban versus placebo in threatened preterm birth: the APOSTEL 8 study. BMJ Open 2019 Nov 26;9(11):e029101.
[68] Nijman TAJ, Goedhart MM, Naaktgeboren CN, de Haan TR, Vijlbrief DC, Mol BW, et al. Effect of nifedipine and atosiban on perinatal brain injury: secondary analysis of the APOSTEL-III trial. Ultrasound Obstet Gynecol 2018 Jun;51(6):806–12.
[69] Kim SH, Riaposova L, Ahmed H, Pohl O, Chollet A, Gotteland J-P, et al. Oxytocin Receptor Antagonists, Atosiban and Nolasiban, Inhibit Prostaglandin F2α-induced Contractions and Inflammatory Responses in Human Myometrium. Sci Rep 2019 Apr 8;9(1):5792.
[70] Marchand G, Blumrick R, Ruuska AD, Ware K, Masoud AT, King A, et al. Novel oxytocin receptor antagonists for tocolysis: a systematic review and meta-analysis of the available data on the efficacy, safety, and tolerability of retosiban. Curr Med Res Opin 2021 Sep 2;37(9):1677–88.
[71] Craciunas L, Tsampras N, Kollmann M, Raine-Fenning N, Choudhary M. Oxytocin antagonists for assisted reproduction. Cochrane Database Syst Rev 2021 Sep 1;2021(12).
[72] Helmer H, Saleh L, Petricevic L, Knöfler M, Reinheimer TM. Barusiban, a selective oxytocin receptor antagonist: placental transfer in rabbit, monkey, and human. † Biol Reprod 2020 Jun 23;103(1):135–43.
[73] Vrachnis N, Malamas FM, Sifakis S, Deligeoroglou E, Iliodromiti Z. The oxytocin-oxytocin receptor system and its antagonists as tocolytic agents. Int J Endocrinol 2011;2011:350546.
[74] Song Z, Albers HE. Cross-talk among oxytocin and arginine-vasopressin receptors: relevance for basic and clinical studies of the brain and periphery. Front Neuroendocr 2018 Oct;51:14–24.
[75] Steinwall M, Bossmar T, Gaud C, Åkerlund M. Inhibitory effects of SR 49059 on oxytocin-and vasopressin-induced uterine contractions in non-pregnant women. Acta Obstet Gynecol Scand 2004 Jan;83(1):12–8.
[76] Steinwall M, Bossmar T, Brouard R, Laudanski T, Olofsson P, Urban R, et al. The effect of relcovaptan (SR 49059), an orally active vasopressin V1a receptor antagonist, on uterine contractions in preterm labor. Gynecol Endocrinol 2005 Feb;20(2):104–9.
[77] Murrell W. Nitro-Glycerine As a Remedy for Angina Pectoris. Lancet 1879;113(2891):113–5.
[78] Smith GN, Walker MC, McGrath MJ. Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. Br J Obstet Gynaecol 1999 Jul;106(7):736–9.
[79] Kim K.H., Kerndt C.C., Adnan G., Schaller D.J. Nitroglycerin. StatPearls. [http://www.ncbi.nlm.nih.gov/pubmed/29494004].
[80] Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R. Randomized double-blind placebo-controlled trial of transdermal nitroglycerin for preterm labor. Am J Obstet Gynecol 2007 Jan;196(1):37.e1–8.
[81] Farina MG, Billi S, Sordelli MS, Ribeiro ML, Di Girolamo G, Lombardi E, et al. Nitric oxide (NO) inhibits prostaglandin E2 9-ketoreductase (9-KPR) activity in human fetal membranes. Prostaglandins Other Lipid Mediat 2006 May;79(3–4):260–70.
[82] Conde-Agudelo A, Romero R. Transdermal nitroglycerin for the treatment of preterm labor: a systematic review and metaanalysis. Am J Obstet Gynecol 2013 Dec;209(6). 551.e1-551.e18.
[83] Duckitt K, Thornton S, O'Donovan OP, Dowswell T. Nitric oxide donors for treating preterm labour. Cochrane Database Syst Rev 2014 May 8.
[84] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. Obstetrics and gynecology. 2016;128(4):e155–64.