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REVIEW ON CURRENT ADVANCEMENTS ON MANAGING PRETERM LABOUR

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ABSTRACT

Preterm birth is the second most leading cause of neonatal death and morbidity after pneumonia. However, the etiology of preterm birth is not fully classified. As reproduction is said to start in the brain, hormonal irregularity is one the main cause of preterm birth with the main culprit being oxytocin. Oxytocin plays a major role in inducing labor and also during lactation. Several tocolytics have been used to prevent or mitigate the effects of preterm labor which are discussed in this paper.

KEY WORDS: Tocolytics, Gestation, Calcium antagonists, Antenatal corticosteroid injection, Amniocentesis.

1. INTRODUCTION

Pre-term birth (i.e.), birth before 37 weeks is the predominant cause of perinatal mortality and morbidity. An array of tocolytics has been used to inhibit pre-term labor and delay pre-term birth. Such agents include NO donors, calcium channel blockers, β mimetics, magnesium sulphate, cyclooxygenase inhibitors and oxytocin receptor antagonists. They are used to delay pre-term delivery long enough to improve neonatal outcome.

1.1. Present situation: Over the past decade, a lot of improvement has been made in this area to save premature babies using feasible cost effective care as in antenatal steroid injection, kangaroo mother care, antiseptic cream for umbilical cord and antibiotics to treat new born infection. Despite all this external assistance, the lower the gestational age, the higher the risk of complication. Thus, prevention of preterm labour using tocolytics could be potentially of tremendous importance. Tocolytics were introduced with a hope that they would prolong the gestational period which will in turn have an important impact on reducing impact of preterm birth.

1.2. Uterus: Uterus is an inverted pear-shaped vital myogenic organ of the female reproductive system. It is occupies the position between the urinary bladder and the rectum. Its main function is to house and nourish the fertilized egg and helps in its growth until delivery. The uterus is divided into four main regions which includes: the fundus a broad upper region where the fallopian tubes joins with the uterus; the body, which is present below the lower end of the fallopian tubes and runs down till the uterine wall narrows down; the third is the isthmus which is the neck region; and the final part, the cervix, extends from the isthmus and opens into the vagina. The uterus is about 6 to 8 cm in length and its is around 2 to 3cm thick. The uterine cavity opens into the vagina, and joins to form the birth canal. The uterine cavity is lined by a mucous membrane called the endometrium which becomes thicker during menstrual cycle and becomes even thicker during egg release from the ovaries. After fertilization the egg attaches to the endometrial wall of the uterus and starts to develop. In case of unfertilized egg, the endometrium, egg and the other tissues is shed off and eliminated from the body as menstrual bleeding. The endometrial fluid's chief constituents include the water, potassium, chloride, iron, sodium and proteins. These provide a favorable condition for the egg and the sperm cells. Three layers of muscular tissue make up the uterine wall which contracts and become thinner as the child develops. After birth the expanded uterus comes to normal size. Until puberty of a female child the uterus is tiny and grows afterwards till menopause, after which there is no chance of becoming pregnant which eventually causes the uterus to become paler and smaller when the female is no longer capable of having children, the uterus becomes smaller, more fibrous, and paler. The uterus is a myogenic organ and is stimulated by electrical activity resulting in membrane depolarization due to intracellular calcium level changes. Apart from hormonal and neuronal control, the GPCRs for controlling uterus stimulation are:

- Oxytocin receptors (OXTR)
- Endothelial receptors
- Prostanoids receptors (PTGER1, PTGFR, TBXAIR)
- Receptors coupled to β adrenoreceptors (ADRB2)
- Prostaglandinoid (PTGDR, PTGER2 and PTGIR)
- Receptors coupled to α_2 adrenoreceptors (ADRA2)
- Muscarinic receptor (CHRM)

Of these, the first three stimulate contractility activating the calcium pathway; the fourth and fifth receptors relax the uterus by stimulating adenylyl cyclase and increasing myometrial cyclic AMP levels; the rest inhibit cyclic AMP production (Kobayashi M, Akahane M,1999).

1.2.1. Hormones involved: Pregnancy is considered to be the combined role of ovary, pituitary and the hypothalamus. Puberty and menopause are events monitored by the brain. The sequence of events is as follows. The hypothalamus secretes Gonadotropin releasing hormone (GnRH). The GnRH triggers secretion of Follicle Stimulating Hormone (FSH) by the pituitary gland. The FSH, in turn stimulates the growth of egg follicles in the ovaries and triggers ovulation. The growing egg follicles manufacture estrogen which is released into blood. Estradiol, a component of estrogen (which is released into the blood by the ovarian follicles) acts on the hypothalamus and causes a change on the production of GnRH, which causes pituitary to produce Leutinizing hormone (LH). LH causes egg follicles to burst and release the ovum. After the egg is expelled, progesterone is produced by the collapsed egg follicle which develops into the corpus luteum. The corpus luteum turns into corpus albicans when there is no fertilization and is flushed out from the body during the menstrual cycle. If fertilization occurs, human Chorionic Gonadotropin (hCG) is released from the placenta which stimulates the progesterone release from the corpus luteum (Margaret A. Shupnik, 1996).

1.2.2. Oxytocin: Oxytocin is a mammalian hypophysial hormone which functions mainly as a neuromodulator. Oxytocin is important for its activity in sexual reproduction during and after child birth. The term oxytocin was coined from two Greek words "oxys" and "tocos" meaning quick birth. Its uterine contracting properties were discovered by British pharmacologist Sir Henry Dale. Oxytocin is a peptide of 9 amino acid sequence: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly. It has a molecular weight of around 1007 daltons. One International Unit (IU) of oxytocin equals 2µg of pure peptide. The mammals have a highly conserved structure of oxytocin. It is mainly released by the pituitary gland and is systemic in function. Oxytocin mainly acts on the brain as well as peripheral hormonal mediated by specific oxytocin receptors. The oxytocin receptor is a GPCR that requires magnesium ions and cholesterol. The OXT gene produces the inactive precursor protein of the oxytocin. This inactive precursor is broken down into smaller fragments by enzymes to yield oxytocin nonapeptide. The oxytocin is produced in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei and stored in the herring bodies at the axon terminal in the posterior pituitary from where it gets released into the blood. In female, oxytocin is synthesized by the corpus leuteum and is involved in endometrial synthesis of prostaglandin $F_{2\alpha}$ along with estrogen to cause regression of corpus leuta. Half-life of oxytocin in blood is 3 minutes (Kobayashi M, Akahane M, 1999).

1.2.3. Mechanism: OT receptors exert their function with the help of Gq/11a class GTP binding proteins which along with Gbg stimulate the activity of the activity of phospholipase C-b isoforms which leads to the generation of inositol trisphosphate and 1,2-diacylglycerol. This inositol trisphosphate triggers calcium release from intracellular stores, while diacylglycerol stimulates protein kinase C, which causes phosphorylation of unidentified target proteins. Finally, an increase of intracellular calcium initiates a variety of cellular events (Kobayashi M, Akahane M,1999). Cellular calcium flux is controlled by the receptor operated and voltage dependent channels. Voltage dependent calcium channels can be classified into four main types. They are:

- L type (Long lasting)
- N type (Neuronal)
- T type (transient)
- P type (purkinji cells)

The P type channels are involved in neuro-transmitter release. Phasic contractions of uterus are inherently dependent on calcium entry through VGCC, particularly of L type, which are present in the plasma membrane of myometrial smooth muscle cells. Calcium induced potassium channels are of two types. They are small conductance and large conductance channels. Large conductance channels are voltage dependent and are found active in the early phases of pregnancy. Small conductance channels are voltage independent and active in late phase of pregnancy. They work by positive feedback mechanism wherein depolarization of calcium channel activates potassium channel which results in hyperpolarization thereby reducing the activity of calcium channel. Small conductance channels due to their exclusive and sensitive regulation by calcium are well suited for modulation of calcium driven uterine contraction (Wimmer G, Pihlstrom BL, 2008).

1.2.4. Metabolism of oxytocin: At the time of parturition oxytocin concentration in the rat uterus increases. Enzymes such as post-proline endopeptidase and aminopeptidase are responsible for the metabolism of oxytocin. Oxytocin molecule can be cleaved at the N terminus or the C terminus. Intrauterine tissues of all mammals contain oxytocinase

activity and thus inactivate oxytocin. This activity is due to opening of ring structure and cleavage of amino acids from the N terminus of linearized molecule by aminopeptidase enzymes. Metabolism at C terminal end of the molecule may be catalyzed by endopeptidase and carboxy peptidase molecule. Therefore the activity of oxytocinase is an important mechanism to regulate the amount of oxytocin available from uterine deciduas.

1.2.5. Progesterone:

1.2.5.1. Cellular signaling: The uterine luminal epithelium (LE) and the superficial glandular epithelia (GE) lack the Progesterone Receptor (PR) and the STAT1 proteins. Hence the non classical pathway is used in the signal transduction of Progesterone. Progesterone increases the production of stromal derived FGF10 and very low levels of HGF that act on the uterine Le/sGE and conceptus trophectoderm cells that express FGFR2(IIIb) and MET receptors for GFG10 and HGF to activate MAPK and PI3K cell signaling (Fuller W. Bazer, Robert C. Burghardt, 2008).

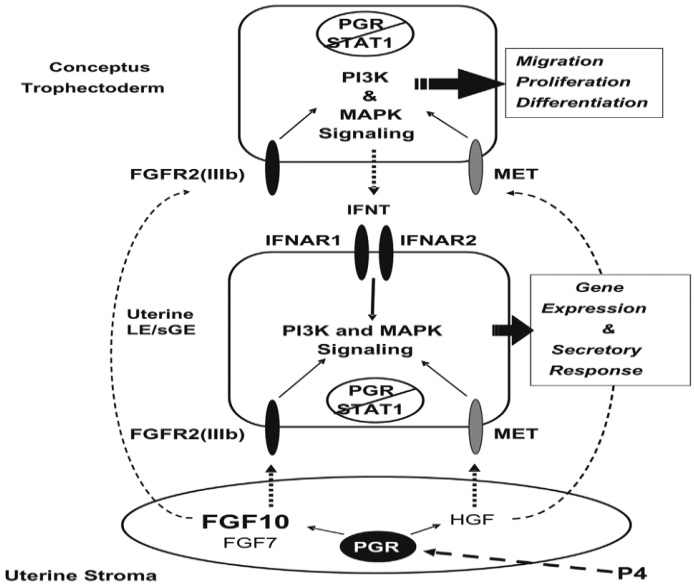

Figure.1.Cell signaling pathway of progesterone

1.3. Preterm Labor: Preterm birth is the most prominent cause of newborn deaths and the second leading cause of deaths after Pneumonia in children under five years. According to WHO preterm is defined as "Babies born alive before 37 weeks of pregnancy are completed". Based on gestational age, they are classified into sub-categories as follows"

- Extremely preterm (<28 weeks)
- Very preterm (28 to <32 weeks)
- Moderate to late preterm (32 to <37 weeks)

According to statistics, every year 15 million babies are born preterm and this number is rising of which, 1 million children each year die due to complication of preterm birth. There are survivors who face a lifetime of disability, including learning disabilities and visual and hearing problems. India tops the chart in being a country with highest incidence of preterm births at 3,519,100 (i.e.) 21% of the total births in the country. The incidence is found to be high in low income economies (Andres Lpoez Bemal, 2007).

Premature babies are those born before completing 37 weeks of gestation period and are often referred as "preemies" who face increased risk of several complications. These premature babies are usually treated in the neonatal intensive care unit (NICU). There are some of the complications listed below:

A. Immature Lungs: The lungs are fully matured in most babies after 36 weeks of gestation. If it is realized earlier that the baby will be delivered in advance before the completion of 36 weeks, then aminocentesis are done to check the maturity levels of lungs. Sometimes steroids are given to speed the development of lungs in the unborn. But the immature lungs seen in the premature babies are generally associated with other respiratory complication as follows.

B. Respiratory Distress Syndrome (RDS): It causes difficulties in breathing because of the absence of surfactant which is responsible to prevent the lungs from in the lungs from collapsing. It is normally treated by supplying supplement oxygen or by employing ventilator, in extreme conditions doses of surfactant is given.

C. Transient tachypnea: This is rapid shallow breathing which occurs in both premature babies and also in fully grown normal babies. In this case mainly intravenous feeding is to be done (Wimmer G, Pihlstrom BL, 2008).

D. Bronchopulmonary Dysplasia (BPD): It occurs due to the deterioration of the baby's lungs. In this case ventilators cannot be used since their lungs are immature and cannot survive the pressure of the ventilators. If they are put on the ventilators there is risk of developing BPD. The preemies take longer time to recover from this condition.

E. Pneumonia: Pneumonia causes inflammation in the region of lungs involved in the exchange of CO_2 and O_2 leading to insufficient supply of oxygen. Treatment often involves the use of antibiotics, supplement oxygen and intubation. In extreme cases can lead to sepsis or meningitis.

F. Apnea and Bradycardia: The absence of breathing is referred to as apnea and bradycardia is the reduction in heart rate. The heart rate can be brought to normal condition by simply rubbing the child's back.

G. Infection: There is a greater risk of infection in premature babies than the normal ones. In order to protect them from infection the premature babies are kept in the incubator.

H. Intraventricular hemorrhage (IVH): There can be a risk of bleeding in the brain of babies born before 34 weeks which can lead to extreme fatal conditions like cerebral palsy, learning difficulties and mental retardation.

I. Immature gastrointestinal and digestive system: Premature newborns the gastrointestinal systems which are not fully developed to absorb the nutrients. So the babies are fed by parentreal nutriotion where the proteins are fed through intravenous route.

J. Anemia: This is caused due to low concentration of RBC in the premature babies than the normal levels of 15g. Treatments involve blood transfusion.

K. Patent Ductus Arteriosus (PDA): This is condition where a blood vessel called ductus arteriosis opens leading to severe cardiac disorder. During the development of the fetus the blood vessel is kept open by the chemical, prostaglandin E to allow the blood flow from lungs to the aorta. During full term labor the levels of the chemical falls causing the blood vessel to close thereby ensuring that the baby requires enough blood from lungs to function properly after birth. But during preterm labor, the prostaglandin E levels are the same which keeps the ductus arteriosus blood vessel open It can be trated by employing medications that reduces the amount of prostaglandin produced.

L. Necrotizing Enterocolitis (NEC): This occurs mainly due to reduced blood supply in the intestine leading to infection in the walls of the intestine. It can be treated by the intravenous administration of antibiotics.

1.3.1. Etiology: Pre-term birth occurs as a result of spontaneous pre-term labour associated with the preterm rupture of membranes and hormonal imbalances, uterine distortions, infections, inflammation, utero placental insufficiency.

1.3.2. Rat Model: Copulation in rats occurs during the later part of the dark cycle (Jeffrey J. Sohmiller, Sonya P. Swing, 2006). Mating behavior is initiated by the males by the genital sniffing of female in estrus and it can by observing the vaginal plug for the presence of sperm in the vaginal smear. Gestation averages 21-23 days from copulation to parturition. The hatched blastocyst is implanted on the 5^{th} day of gestation and is regulated by the maternal estrogen since the rat embryo does not produce estrogen. During the first half of pregnancy, progesterone is produced by the ovary stimulated by prolactin surges induced by the coitus. During the second half of pregnancy, progesterone is also produced by the placenta. The corpus leuteum is activated and sustained by the progesterone. The placenta does not produce estrogen and the progesterone produced is not sufficient to cause pregnancy. Placentation in rat is usually discoidal and hemochoreal. Discoid placentation increases circular area of attachment between the fetal and maternal tissues. In Hemochoreal placentation the fetus comes in direct contact with the maternal blood by the invasion of the fetal trophoblast with the maternal blood vessels. The placental lactogens are polypeptides produced by the placenta in order to stimulate the development of mammary gland as well as the corpus leuteum to secrete progesterone. 5 days prior to parturition, the mess building behavior of the female rats starts and is maintained throughout lactation. By day 17 of gestation, the pubic symphysis begins to relax and is completed before the onset of parturition. During the second half of pregnancy the cervix begins to extend with help of the hormone called relaxin produced by the corpus leuteum (Wimmer G, Pihlstrom BL, 2008). The mechanism responsible for stimulating parturition cannot be fully understood. It has been understood that

the increase in the secretion of ovarian estrodiol during the final day of gestation may be due to the action of estrogen. The birth of the pups can be identified by the presence of vaginal discharge 1.5-4 hours before delivery. During labor the female assumes a semi crouched position by extending the body and resting the abdomen on the floor of the cage and starts licking the vulva. The time required for the delivery process varies with litter size and usually ranges from 55 minutes to nearly 4 hours with an average of 1.5 hours

The female rat contains six pairs of mammary glands and nipples with three pairs in the thoracic region and the other three pairs in the abdomen. These extend during the lactation period which is around 2 weeks and requires suckling for maintenance. The use of prolactin and glucocorticoids initiates the lactation while the level of corticosterones increases during the final days of gestation. The placental hormone influences the development of mammary gland and lactogen plays role in the maintenance of milk production. The oxytocin is released from the pituitary by activating the neuro endocrine loop which leads to the contraction of myo-epithelial cells for the ejection of milk.

1.3.3. Survey of Drugs Available: The physiological trigger for labor both at term and preterm remains a mystery. At term, judging whether or not labor has started depends on the frequency of contractions and cervical dilation. Judging whether or not preterm labor has started is more difficult because contractions may occur without cervical dilation, and waiting for the cervix to dilate may lead to stronger contractions, which are more difficult to stop. Successful inhibition of preterm labor depends upon early diagnosis, but the diagnosis of preterm labor is erroneous up to 80% of the time. As a result, preterm labor is widely overdiagnosed so as not to miss those minorities of cases of true preterm labor. Over the years, a wide variety of drugs—called tocolytics—have been used in attempts to suppress preterm contractions. The effectiveness of several of these drugs is discussed below.

A. Betamimetics: Betamimetic agents are used more extensively than any other agents. All of these drugs are chemically and pharmacologically related to the catecholamines, compounds in the body that control involuntary muscles such as the heart and uterus. These drugs stimulate receptors in the uterus which cause the uterus to relax, thus stopping uterine contractions. Data on the effect of betamimetic drugs in controlled trials of preterm labour shows that they are successful in delaying delivery for up to two days. However, there is no associated decrease in the incidence of perinatal mortality or morbidity with the use of these drugs. One of the major benefits of using tocolytic drugs is to delay delivery long enough to give prenatal corticosteroids a chance to enhance the maturation of fetal lungs. One may conclude that, conversely, little benefit may be reaped if glucocorticoids are not used. Recent attention has been focused on a new way to administer the betamimetic drugs which uses a pump implanted under the skin to inject the drugs. The pump delivers small doses of the drug in short pulses, a method that is thought to maximize the effect of each small dose. Pregnancy was prolonged an average of nine weeks in a small group of women who failed oral betamimetic therapy, but used the pump. Further studies are needed to validate this potentially promising approach.

B.Inhibitors of Prostaglandin Synthesis: There is substantial evidence that prostaglandins are of critical importance in the initiation and maintenance of human labor. Suppression of the body's ability to produce prostaglandins is, therefore, a logical approach to the prevention of preterm labor. The most widely used inhibitor of prostaglandin synthesis in preterm labor is indomethacin. Two small studies found that the prostaglandin-inhibiting drugs may be effective in preventing preterm labor.Compared with betamimetic drugs, indomethacin is more effective in delaying delivery for up to two days. In addition, indomethacin delayed delivery slightly longer (7 to 10 days) than betamimetic drugs, and decreased the overall incidence of preterm delivery and low birth weight. One of the major reasons prostaglandin inhibitors are not more widely used is that they are not innocuous drugs. In the mother, side effects such as stomach ulcers, gastrointestinal and other bleeding, and allergic reactions occur but are very rare. In the fetus, indomethecin has been associated with a severe interruption in the blood circulation between the baby's heart and lungs, and other serious side effects.

C.Magnesium Sulfate: Magnesium sulfate is a commonly used tocolytic, and in many institutions is the first-line therapy for preterm labor. The ability of magnesium to decrease uterine contractility has long been recognized, but the mechanism by which it does so is not known. In one trial, magnesium was found to have no significant effect on duration of gestation, birth weight, neonatal morbidity, and perinatal mortality. However, magnesium sulfate appears to be no better than other tocolytics. The combination of ritodrine (a commonly used betamimetic drug) and magnesium sulfate resulted in a higher incidence of serious side effects with no greater benefit than ritodrine alone. There are no convincing data that magnesium sulfate delays delivery beyond two days, nor are there data to show a decrease in preterm delivery or an improvement in neonatal outcomes beyond that gained by glucocorticoid administration.

D.Calcium Antagonists: Over the past 10 years, calcium channel blockers like nifidipine have emerged as major agents for the control of preterm labor and for the treatment of hypertension in pregnancy. Because calcium is required to

produce muscle contractions, agents that block the uptake of calcium in muscle cells will decrease the ability of the muscles to contract. nifedipine, the most commonly used calcium blocker, has been as successful as betamimetics in delaying preterm labor. As with the betamimetics, magnesium sulfate, and indomethacin, there has been no real evidence for decreased perinatal morbidity and mortality with the use of calcium antagonists.

E.Combination Therapy: As all tocolytics have significant failure rates, especially in the face of advanced preterm labor, several groups have asked whether combination therapy may offer advantages. One randomized trial compared ritodrine alone with ritodrine and magnesium sulfate and found improved pregnancy prolongation with the combination therapy. Unfortunately, in two studies, one-half of the women receiving combination therapy developed severe side effects (cardiovascular symptoms or very fast heart rates). Most clinicians are reluctant to accept this high level of side effects given the small benefit that even single-agent therapy has shown. A combination that may have more benefit in the future is that of betamimetics and calcium channel blockers, which is currently under study.

F. Oxytocin Analogues: Recently, an oxytocin analogue which also blocks uterine contractility has been introduced. Oxytocin is a compound that the body produces to stimulate uterine contractions. Oxytocin analogues may be used to prevent the action of oxytocin and thus prevent contractions. Further studies are needed to determine the efficacy of these promising drugs. Atosiban is a synthetic peptide which is a competitive antagonist of oxytocin at uterine oxytocin receptor is being used as a tocolytic for delaying the onset of preterm labour. Although it is comparatively less effective than b2 agonists, it is still preferred because of its better tolerance and has reduced cardiovascular side effects. However, the adverse effects of using atosiban include Nausea, Headache, Dizziness, Tachycardia and U.T.I in mother and faetal tachychardia in the child (Kashanian M, Akbarian AR, 1996).

1.3.4. Preclinical evidence: The in-vivo study of the tocolytic activity of the *Syzygium cumini* seed extract is based on the results obtained by the in-vitro study of the extract on the smooth muscle of the uterus. The in-vitro study was carried out by sacrificing the rat and the uterine horn was isolated and placed in De Jalon solution which was aerated with oxygen. The physiological condition required for the tissue was provided and the response of the tissue on KCl induced contraction was studied using the kymograph instrument. The KCl induced maximum contraction in the uterus smooth muscle strip but it was inhibited by the action of the *Syzygium cumini* extract on the muscle strip. The maximum inhibition of contraction was 55% against 100% of KCl. The maximum contraction of the KCl may be due to the K^+ ion which promotes the influx of Ca^{2+} into the cell. The extracellular K^+ ions influences the ATP sensitive potassium channel which leads to the increase in the intracellular K^+ concentration. This prevents the hyperpolarisation of the cellular membrane and also increases the cytosolic calcium. The relaxation produced by the *Syzygium cumini* extract shows the tocolytic effect which helps in preventing preterm premature rupture of the uterus membrane thereby avoiding preterm delivery.

Hence taking this result as a base the tocolytic activity of the extract is studied in in-vivo study (Archana N, Ramasamy M, 2012)

2. CONCLUSION

Currently, there is no evidence for the fact that the use of tocolytic drugs is effective in preventing preterm birth. Moreover, the use of these drugs is associated with many potentially severe side effects. There is strong evidence that tocolytic agents work to delay delivery for up to two days. This short delay is important as it can be used to allow time for corticosteroids to take effect and enhance fetal lung maturity, or to allow the mother to be transferred to a hospital with high-level neonatal intensive care facilities. The scientific evidence of efficacy available for all of these drugs is surprisingly scarce given the frequency of their use. There are few data to support using tocolytics without prenatal corticosteroid therapy to achieve a measurable decrease in perinatal morbidity and mortality. Despite the availability of tocolytic agents and their extensive use, no reduction in the overall incidence of low birth weight (less than 2,500 grams, or 5 pounds, 8 ounces) has been recorded since the introduction of these drugs. In many instances of preterm labor, the use of tocolytic drugs is contraindicated, such as with uterine infections, bleeding, or severe maternal disease and, therefore, these drugs cannot be used. Thus, despite the short-term efficacy of tocolytic drugs, this technology has not made an impact on reducing overall low birth rate.

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