

**Review Article****Predictors, Treatment and Prevention of Preterm Labour: A Review**Khairun Nahar<sup>1</sup>, Khodeza Khatun<sup>2</sup>

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**Abstract**

Preterm labour (PTL) is one of the leading causes of neonatal morbidity and mortality throughout the world. It is also a major public health problem for its long-term disabilities like cerebral palsy and visual disturbance. Preterm labour is a multifactorial problem and its overall global incidence is 11.1 per 100 live births with a significant regional variation. About 45-50% of preterm deliveries are spontaneous, 30% are associated with preterm prelabour rupture of membranes (PPROM) and another 15-25% is induced for maternal and/or foetal risk. Previous history of PTL is an important risk factor; risk is 14.3% after one preterm birth and 28% after two preterm births. Other important risk factors are multiple pregnancy, polyhydramnios, bicornuate uterus, cervical incompetence & bacterial vaginosis. Prediction of PTL is very difficult but identification of risk factors, assessment of cervical length by ultrasonography and detection of foetal fibronectin in cervical secretions are of great help. Advanced cervical dilatation (>3 cm) or PPRM associated with sufficient and frequent uterine contractions confirm the diagnosis of preterm labour. Prevention of PTL has been tried with prophylactic cervical cerclage, antibiotics and progesterone. PTL is treated with various tocolytic agents and glucocorticoids and antibiotics for local or systemic infection. Betamimetics, calcium channel blockers (nifedipine), prostaglandin synthesis inhibitors and magnesium sulfate are the commonly used tocolytics. Nifedipine has significantly fewer maternal adverse effects than betamimetics and magnesium sulphate. Antenatal corticosteroid treatment has been found to lower neonatal mortality, the risk of neonatal respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis. The ultimate goal of prevention and management of preterm labour is to improve neonatal outcome and to reduce morbidity and mortality. [Journal of Science Foundation, July 2017;15(2):57-63]

**Keywords:** Preterm labour, prediction, prevention, treatment**1.0. Introduction**

Preterm labour (PTL) means the onset of sufficient uterine contractions with progressive dilatation and effacement of cervix between 20 and 37 completed weeks of gestation. A systematic review has estimated a worldwide incidence of PTL 11.1 per 100 live births with a significant regional variation (Tielsch 2015). The majority (85%) of global preterm births has been identified in Asia and Africa (Beck et al., 2010). Unfortunately, accurate and complete population-based data and medical records are not available in developing countries like ours. In a rural Bangladeshi cohort the rate of PTL was found 22.3% of total live birth (Shah et al., 2014). It is an important cause of neonatal and infant mortality, often as a result of respiratory distress syndrome due to immaturity of lung. Babies who survive are also at high risk of various types of neurological disability and visual problems. Preventing preterm delivery is a great challenge in

<sup>1</sup>Associate Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

<sup>2</sup>Assistant Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

**Correspondence:** Associate Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Cell no.: +8801713049088; Email: [khrrnhr@yahoo.com](mailto:khrrnhr@yahoo.com)

obstetric practice worldwide. The etiology of preterm delivery is unclear, but is multifactorial and influenced by genetic and environmental factors. Women with previous preterm labour are at increased risk in subsequent pregnancies. Risk of PTL in subsequent pregnancies is 14.3% after one and almost double after two preterm births (28%) (Bakketeig et al., 1979). Increased rate of preterm delivery is also noted among the group of women delaying pregnancy and using assisted reproductive technology (Wright et al., 2006). About 45-50% of preterm deliveries are spontaneous labour with intact membranes, 30% are associated with preterm prelabour rupture of membranes (PPROM) and another 15-20% is iatrogenic (Pennell et al., 2007). Iatrogenic factors include termination of pregnancy by elective caesarean section or induction of labour due to medical indications like pregnancy induced hypertension, abruptio placenta, intra-uterine growth restriction, or nonreassuring foetal surveillance. It is a major public health problem especially with high incidence of neonatal mortality and long-term disability. The care of the preterm babies is very expensive and these are the main cause of increased neonatal mortality in developing countries. Prevention, early diagnosis and effective management of PTL can improve neonatal outcome and have a great impact on social and long-term public healthcare costs.

## 2.0. Prediction of the Preterm Labour

Prediction of PTL is difficult, but the following factors have been taken into consideration as important predictors.

1. Presence of risk factors
2. Bacterial vaginosis (BV)
3. Presence foetal fibronectin (FFN) in cervico-vaginal secretion.
4. Shortening of cervical length.

**2.1. Risk Factors of Preterm Labour:** A previous history of preterm labour is the most important risk factor. Other risk factors include multiple pregnancy, uterine over-distension due to polyhydramnios or macrosomia, uterine anomalies like bicornuate uterus, cervical incompetence or previous cervical surgery, cervical inflammation as a result of bacterial vaginosis (BV) or trichomoniasis, bleeding in early pregnancy, cigarette smoking, poor socioeconomic or educational status, and young or advanced maternal age.

**2.2. Bacterial Vaginosis (BV):** Bacterial vaginosis means the alteration of normal bacterial flora of the vagina, where lactobacilli are replaced by anaerobic organisms. About 10-25% of pregnant women may have BV and half of them remain asymptomatic (Ugwumadu et al., 2004). An association has already been identified between BV and preterm labour and it has been found to increase the risk of preterm labour by two-folds (Leitich et al., 2003).

**2.3. Foetal Fibronectin:** It is a basement membrane protein, produced by foetal membranes acts as an 'adhesion binder' which facilitates the attachment of the placenta and membranes to the decidual layer of endometrium. This foetal fibronectin is normally found in cervical secretions up to 20 weeks of gestation. Presence of FFN in cervical secretions after 24 weeks is an indication of disruption of membranes due to inflammation which usually precedes the onset of PTL. One meta-analysis has revealed high negative predictive value of FFN (Leitich et al., 2003). The specificity of FFN test for predicting preterm delivery within 1 to 3 weeks was found 89.0% to 92.0%. The sensitivity of the test in predicting the onset of preterm labour within 1 week and 3 weeks was found 71.0% and 59.0% respectively.

**2.4. Cervical length assessed by USG:** Cervical competence is essential for maintaining the uterine contents till full term and one of the earliest indicator of incompetence or onset of labour is shortening of cervix. Iams et al (1996) established the normal cervical length patterns after 22 weeks of pregnancy. An increased relative risk of PTL with cervical length of < 25 mm after 24 weeks of pregnancy has been found with wide variation in the predictive values with sensitivity 68.0 to 100.0% and specificity 44.0 to 79.0% (Leitich et al., 1999). Cervical length which is shorter than 25 mm has been demonstrated by transvaginal ultrasonography at 22 to 25 weeks in 20.0% of high-risk women with a history of one or more spontaneous preterm births (Durnwald et al., 2005). Isolated cervical length assessment is not supported with strong evidence in routine practice but it has a vital role in high risk group.

**2.4.1. Combination of FFN Test and Cervical Ultrasonography:** Cervical length less than 25 mm between 24-28 weeks and positive FFN test result in women with high risk of preterm labour are useful predictors of PTL (Edwin-Chandrarahan 2005).

## 3.0. Diagnosis of Preterm Labour

Regular and frequent uterine contractions with sufficient intensity associated with progressive effacement and dilation of the cervix are indicative of active preterm labour. The cervical changes can be ascertained by digital vaginal examination. In suspected cases of PTL, it may be practical to obtain a sample of vaginal secretion for foetal fibronectin (FFN) before digital examination of the cervix. Advanced cervical dilation (>3 cm) or PPROM associated with regular and sufficient uterine contractions confirm the diagnosis of preterm labour. If the diagnosis remains in doubt after the examination, only then the FFN specimen can be sent for analysis. A FFN concentration of  $\geq 50$  ng/mL has been established as the best threshold to define a positive test result.

#### 4.0. Treatment of Preterm Labour

The aim of prolonging the pregnancy is to improve the neonatal outcome. Prolongation of pregnancy at least for 48 hours is an important objective, so that foetal lung maturation can be induced with glucocorticoids and the pregnant woman can be transferred to a high-level perinatal care facility, if needed. These two measures have been successfully improved the survival rate in babies born before 34 weeks.

#### 4.1. Therapeutic Measures

- Inhibition of uterine contraction with drugs
- Glucocorticoid administration to promote foetal lung maturation
- Antibiotics to treat local infections, if present
- Avoidance of physical exertion- bed rest and hospitalization

#### 4.2. Inhibition of uterine contractions with drugs—tocolysis

Tocolytic therapy should be continued for shortest possible duration and promptly terminated once contractions have stopped. In routine clinical practice there is no indication for continuing tocolytic therapy for more than 48 hours except placenta praevia. Chorioamnionitis and malformed foetus are contraindications of using tocolytics. There is no agent of first choice but the most effective and having the least side effects is selected for individual patient. Although aggressive tocolysis is not usually used beyond 34 weeks of gestation, it is better not to deliver patients at this gestation without specific indication because of a higher risk of neonatal morbidity in infants born before 37 weeks gestation (Cheng et al., 2011).

**Table 1: Tocolytics Drugs used in Clinical Practice**

Substance class	Active substances
Betamimetics	Terbutalin, ritodrine, fenoterol
Calcium antagonists	Nifedipine
Inhibitors of prostaglandin synthesis	Indomethacin
Magnesium sulphate	Nitroglycerin
NO donors	
Oxytocin-receptor antagonists	Atosiban

**4.2.1. Betamimetics:** agents like terbutaline and ritodrine, were the agents of choice in past, but recently their use has been significantly diminished due to potential maternal and fetal side effects. Among all tocolytics betamimetics have the highest side-effect rates. The maternal side effects include severe cardiac arrhythmia and pulmonary oedema, fatality has also been reported in a prospective cohort study. According to a Cochrane meta-analysis of eleven placebo-controlled trials of ritodrine and terbutaline can prolong the pregnancy by 2-7 days, but do not lower perinatal mortality (Anotayanonth et al., 2010).

**4.2.2. Calcium antagonists:** This has been proved to be effective and safe drugs for treatment of PTL. In the Royal College guidelines these have been preferred above all other tocolytics because of their effectiveness and tolerability. A systemic review by Conde-Aquedo et al (2011) revealed significantly fewer maternal adverse effects of nifedipine than  $\beta_2$ -adrenergic-receptor agonists and magnesium sulphate. Side effects are nausea, headache, palpitations, and reflex tachycardia. Nifedipine has been proved to lower the frequency of neonatal intraventricular hemorrhage (OR 0.53; 95% CI 0.34–0.84), respiratory distress

syndrome (OR 0.63, 95% CI 0.46–0.86) and necrotizing enterocolitis (OR 0.21, 95% CI 0.05–0.94) (de-Heus et al., 2009). Recommended dosage of nifedipine is initial two doses of 20 mg orally with 30 minutes interval, and then continued with 20 mg 3 to 8 hourly for the next 48 to 72 hours with a maximum dose of 160 mg/d. If needed after 72 hours, long-acting nifedipine 30 to 60 mg daily can be used.

**4.2.3. Inhibitors of prostaglandin synthesis:** indomethacin, is the best-tested agent in this class, has similar efficacy to betamimetics but fewer maternal side effects. But it has potential foetal risks of premature closure of ductus arteriosus with persistent pulmonary hypertension, foetal oliguria or anuria. A meta-analysis of the effect of antenatal indomethacin on neonatal outcomes revealed no association with neonatal respiratory distress syndrome or intraventricular hemorrhage, but revealed an elevated risk of periventricular leukomalacia (OR 2.0, 95% CI 1.3–3.1) and early necrotizing enterocolitis (OR 2.2, 95% CI 1.1–4.2) (Amin et al., 2007).

**4.2.4. Magnesium sulphate:** is used as the primary tocolytic agent because of its better tolerance as well as neuroprotecting effects on foetus. Common maternal side effects are nausea, headache, drowsiness, and blurring of vision in therapeutic dose. Toxicity includes maternal and even foetal respiratory depression. A Cochrane meta-analysis of 23 trials failed to document efficacy for the prolongation of pregnancy by 48 hours (Conde-Agudelo et al., 2009). Several studies on antenatal magnesium sulfate for preterm labor have reported a decreased risk of cerebral palsy in preterm infants. However, in 2013, the FDA issued a warning against continuous use of IV magnesium sulfate for more than 5 to 7 days.

**4.2.5. NO donors:** nitroglycerine has been used as the NO donor in all clinical trials in the treatment of PTL with some conflicting results. The transdermal nitroglycerin was reported to be safe for the mother and the fetus by Schleussner et al (2003). A small Indian study has revealed the efficacy of transdermal nitroglycerine patch in delaying delivery for 48 hours. Whereas a Cochrane database review concluded that there is insufficient evidence to support the routine use of nitric oxide donors in the treatment of threatened preterm labour.

**4.2.6. Oxytocin antagonists: atosiban** is an antagonist of oxytocin and used as a tocolytic agent through intravenous route. According to a meta-analysis of nine randomized trials, atosiban was found as effective as betamimetics, and its side-effect rate is less than 1.0%. A systematic review of 14 RCTs demonstrated no superiority of atosiban compared with betamimetics or nifedipine in prolonging the pregnancy or neonatal outcomes, although atosiban showed less maternal adverse effects (Flenady et al., 2014).

### 4.3. Induction of Lung Maturation with Glucocorticoids

Glucocorticoids help in maturation of foetal lungs and are often administered during preterm labor. Steroids help the lungs mature and promote the production of surfactant; a substance which prevents the alveoli to collapse. Steroids also reduce the risk of intraventricular hemorrhage and other complications affecting the bowels and circulatory system of preterm babies. Steroids are usually used in all women before 34 weeks of gestation. Betamethasone is the most widely used steroid and for the greatest benefit it is given at least 48 hours before delivery. The dosage schedule consists of two doses of betamethasone 12 mg intramuscularly at 24 hours interval or four doses of dexamethasone 6 mg intramuscularly at 12 hours interval. Corticosteroid treatment has been demonstrated to reduce neonatal mortality (OR 0.69, 95% CI 0.58–0.81), neonatal respiratory distress syndrome (OR 0.66, 95% CI 0.59–0.73), intraventricular hemorrhage (OR 0.54, 95% CI 0.43–0.69), and necrotizing enterocolitis (OR 0.46, 95% CI 0.29–0.74) (Leitich et al., 1999). Though steroid is usually used before 34 weeks, a recent study described a benefit of steroid in late preterm (34 to 37 weeks) also. Accordingly the American Congress of Obstetricians and Gynecologists (ACOG 2016) issued a practice advisory that administration of betamethasone may be considered in women with a singleton pregnancy between 34 and 37 weeks gestation at imminent risk of preterm birth within 7 days.

### 4.4. Treatment of Local Infection with Antibiotics

Vaginal infections are considered to be an important cause of preterm labour and PROM. Treatment of vaginal infections with antibiotics is considered mostly to reduce the risk of maternal and foetal infections and to halt the process of PTL. A meta-analysis of 22 studies done with women having PPROM showed the benefits of antibiotics to reduce the frequency of chorioamnionitis (OR 0.66, 95% CI 0.46–0.96) and to prevent preterm birth within 48 hours to 7 days (Kenyo et al., 2010). Antibiotics given with intact membranes can reduce the rate of maternal infection (OR 0.74, 95% CI 0.64–0.87), but have no role on prolongation of pregnancy or reduction of the rate of neonatal complications and thus the routine administration of antibiotics in preterm labour is not recommended currently.

#### 4.5. Bed Rest and Hospitalization

All women in preterm labor should be hospitalized for close monitoring and to take appropriate measures to stop labour. There is no statistical evidence that bed rest can actually decrease the rate or stop the preterm labour. A systematic review on the effect of bed rest for multiple pregnancies revealed no benefit (Crowther and Han 2010).

#### 4.6. Delivery

Delivery of the preterm infant involves some specific measures to ensure the well-being of newborn specially avoidance of any intracranial trauma. ACOG has suggested a policy of delayed cord clamping which increases newborn hemoglobin and reduces rates of intraventricular hemorrhage, necrotizing enterocolitis and required transfusions. ACOG specifically recommends a delay in umbilical cord clamping for at least 30–60 seconds after birth of preterm babies not requiring immediate resuscitation (Crowther and Han 2010).

#### 5.0. Prevention of Preterm Delivery

Prevention of PTL is great challenge in obstetric practice throughout the world. Many strategies have been tried according to various clinical situations as well as availability of neonatal care facilities. Many studies on the prevention of premature labour have been done, and the Cochrane database alone contains 17 meta-analyses on the subject. Prevalence of premature labour can be lowered by improving maternal health and by avoiding risk factors before or during pregnancy. The ultimate goal of prevention is the early identification of pregnant women at risk and to take necessary steps so that pregnancies can be carried to term. Many clinical interventions to prevent PTL have been attempted with antibiotics, tocolytics, progesterone and cervical cerclage (Kenyo et al., 2010).

**5.1. Antibiotics:** Intra-uterine infection and inflammation play important role in the etiology of spontaneous preterm labor, particularly before 32 weeks or the pregnancies complicated by PPROM. Associations between bacterial vaginosis and preterm birth are well-established for several decades. Role of antibiotics for prevention of PTL is largely controversial. A Cochrane Review concluded that there is no clear overall benefit from prophylactic antibiotics in preterm labour with intact membranes on neonatal outcome. The ORACLE trial showed that the use of antibiotics in patients with PPROM reduces neonatal morbidity, but not the incidence of preterm birth (Crowther and Han 2010). Macrolide antibiotics, commonly used for bacterial vaginosis are ineffective against *Ureaplasma* and *Mycoplasma* spp., which are most frequently associated with preterm birth. There are some evidences, that antibiotic treatment in early pregnancy may be more effective in preventing preterm birth in selected cases. Lamont and colleagues have shown that administration of clindamycin to women with abnormal vaginal flora before 22 weeks gestation may reduce the rate of subsequent preterm birth.

**5.2. Progesterone:** Progesterone has been tried for many years in several formulations for the prevention of PTL. Here synthetic progesterones are avoided due to androgenic side-effects and natural progesterone is used in oral, vaginal or parenteral routes. A multi-centre randomized controlled trial concluded that prophylactic use of 17-hydroxy progesterone caproate can significantly reduce the incidence of preterm labour but is not useful in established PTL. Meta-analysis of RCTs has revealed progesterone can significantly reduce the incidence of both early and late PTL. Progesterone treatment has been proved with strong evidence that it may prevent preterm birth in women with short cervix diagnosed at mid-pregnancy. A meta-analysis of five trials has shown that vaginal progesterone given in women with short cervix is associated with a significant reduction in the rate of preterm birth neonatal complications including respiratory distress syndrome (Kenyo et al., 2010).

**5.3. Cervical Cerclage:** There is no clear evidence to support routine practice of prophylactic cervical cerclage for all women at risk of PTL but has been tried to prevent preterm delivery in women with ultrasonographic evidence of short cervix. One multi-centre randomized controlled trial using cervical length of 15 mm as a cut-off point concluded that cervical cerclage in women with short cervix does not significantly reduce the risk of early preterm delivery (Kenyo et al., 2010). The role of emergency cerclage with bulging membranes to prevent impending preterm birth is very much controversial although some studies reported a median prolongation of pregnancy for 4.5 weeks after the procedure. Use of emergency

cerclage along with indomethacin, antibiotics and bed rest has been documented to reduce preterm delivery before 34 weeks in comparison to only bed rest and antibiotics. However, one meta-analysis has revealed the effectiveness of cerclage on a high-risk group of pregnant women after previous preterm birth and has a short cervix in mid-pregnancy.

## 6.0. Conclusion

Preterm labour is a multifactorial condition with a high risk of neonatal mortality as well as both short and long term morbidity. Proper prediction, prevention, early diagnosis and specific treatment of preterm labour are essential to improve survival and quality of life of the newborn. As the cause of PTL is still largely unclear, it is difficult to predict, prevent and treat. Treatment of preterm labour is mainly antibiotics, tocolytics and glucocorticoids with varying success. Unfortunately, there is still much confusion regarding the ideal tocolytic drug with minimum maternal and foetal side effects. The goal of management of preterm labour is to increase the chance of survival of neonate, to improve the quality of life and to reduce the public health-care cost.

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