

# Preterm Labor: A Review

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## Abstract

*Introduction:* Preterm labor (PTL) is one of the leading causes of perinatal morbidity and mortality. It is one of the major public health problems, especially with reference to mortality, disability and health care expenses.

*Incidence:* The overall incidence of PTL is around 10-15% (6-15% Range)<sup>3</sup> (The incidence of PTL in our institute (JNMC) was 10.2% during 2006-2007. Out of all PTL 50% occur spontaneously, 25% following preterm prelabor rupture of membranes (PPROM) and another 25% iatrogenic (Induced due to maternal and/or fetal risks).

*Risk factors:* Previous history of preterm labor is one of the important risk factor (risk of PTL in subsequent pregnancies is 14.3% and 28% after one and two preterm births. Others include multiple pregnancy, uterine over distension (polyhydramnios, macrosomia and fibroids), uterine anomalies, cervical incompetence, bacterial vaginosis, bleeding in early pregnancy, poor socioeconomic status, elderly and adolescent age group and tobacco use.

*Predictors :* Cervical length assessment by USG, fetal fibronectin, vaginal pH are being used.

*Prevention:* Progesterone and clindamycin (abnormal vaginal flora) antibiotic is being used with reasonable evidence.

*Treatment:* Corticosteroids and antibiotics help in reducing neonatal morbidity and mortality and tocolytics (nifedepine and atosiban are recommended) helps in allowing the steroids to act.

*Newer developments:* New predictors like higher vaginal pH (> 4.5) and Gram stain score of 9 to 10 with Nugent criteria in early pregnancy is increasingly associated with preterm labor. Search for selective and safe tocolytic is also under consideration, specially the prostaglandin synthetase inhibitors and the role of potassium channels in myometrium.

*Conclusion:* Successful prediction, prevention and treatment of preterm labor has significant influence on the perinatal outcome, health care expenditure and quality of life. As the cause for preterm labor is still an enigma, it is difficult to predict, prevent and treat PTL successfully. At present the treatment of PTL is mainly antibiotics, tocolytics and corticosteroids with varied success.

**Keywords:** Preterm labor (PTL), preterm birth, predictors of PTL, tocolytics.

## INTRODUCTION

Preterm labor (PTL) is one of the leading causes of perinatal morbidity and mortality. It is one of the major public health problems, especially with reference to mortality, disability and health care expenses. This problem in a country like India has different magnitude, as the cost involved in caring these preterm babies is enormous, which is not within the reach of the poor.<sup>1</sup>

Unfortunately there is very little change or no change in the incidence of PTL in the last half century. Effective preventive and therapeutic measures are still not available because of the persistence of uncertainties of measures to prevent/treat preterm labor.

Effective strategy for both prevention and management can definitely improve the perinatal outcome.

This review is an attempt to provide an update on preterm labor.

## DEFINITION

Occurrence of regular uterine contractions (four or more in 20 minutes or eight or more in 1 hour) and cervical changes (effacement equal to or greater than 1 cm) in women with intact fetal membranes and gestational age less than 37 weeks.<sup>2</sup>

## HOW SERIOUS IS THE PROBLEM?

The overall incidence of PTL is around 10-15% (6-15% Range)<sup>3</sup> (The incidence of PTL in our institute (JNMC) was 10.2% during 2006-2007. Out of all PTL 50% occur spontaneously, 25% following preterm prelabor rupture of membranes (PPROM) and another 25% iatrogenic (Induced due to maternal and/or fetal risks). It is leading cause of neonatal death and disability (both short-term and long-term) especially cerebral palsy, deafness, blindness and chronic lung disease. The care of the preterm babies is highly expensive and not within the reach of the poor, this is one of the main reasons for increased mortality in developing countries.

## CAN WE PREDICT THE PRETERM LABOR?

The answer to this question is to a large extent no, but there have been attempts to predict preterm labor taking into consideration the following factors.

1. Risk factors.
2. Fetal fibronectin (FFN).
3. Bacterial vaginosis.
4. Cervical length assessment by USG.

### RISK FACTORS

Previous history of preterm labor is one of the important predictor as it is estimated that the recurrence risk of PTL in subsequent pregnancies is 14.3% after one preterm birth and it is almost double with two preterm births (28%).<sup>4</sup>

The other risk factors are:

1. Multiple pregnancy.
2. Uterine over distension (polyhydramnios, macrosomia and fibroids).
3. Uterine anomalies.
4. Cervical incompetence.
5. Bacterial vaginosis.
6. Bleeding in early pregnancy.
7. Poor socioeconomic status.
8. Elderly and adolescent age group.
9. Tobacco use (smoking and smokeless).

However these risk factors have variable sensitivities and predictive values.

### FETAL FIBRONECTIN

It is a basement membrane protein, acts as an 'adhesion binder' (facilitates the attachment of the placenta and membranes to the uterine decidua) produced by fetal membranes. This fetal fibronectin is normally detectable up to 20 weeks of gestation in cervical secretions. Presence or detection of FFN in cervical secretions after 24 weeks is indication of disruption of membranes due to inflammation that usually precedes the onset of PTL. FFN has high negative predictive value as (absent FFN co-relates with very less chance of PTL) revealed by meta-analysis.<sup>5</sup> This suggests that a negative FFN rules out imminent PTL, where as positive FFN test has lower specificity indicating that the woman may go into PTL.

### BACTERIAL VAGINOSIS (BV)

Infection is closely associated with PTL in almost 20-40 % of cases.<sup>2</sup> Abnormal bacterial vaginal flora earlier in gestational age is associated with earlier onset of PTL. Normal bacterial flora of the vagina (Lacto bacilli) is replaced with abnormal organisms in BV. Results of screening for BV for prediction of PTL are inconclusive and benefits are not clear especially in low risk group.<sup>6</sup>

## CERVICAL LENGTH ASSESSMENT BY USG

Cervical competence is an important factor maintaining the uterine contents till full term and one of the earliest indicator of incompetence or onset of labor is shortening of cervix. Iams et al established the normal cervical length patterns after 22 weeks of pregnancy.<sup>6</sup> There is an increased relative risk of PTL with cervical length of < 25 mm after 24 weeks of pregnancy with wide variation in the predictive values (sensitivity 68-100% and specificity 44-79%)<sup>8</sup> Isolated cervical length assessment routinely is not supported with strong evidence. However in high risk pregnancies it has a role.

Together fetal fibronectin and cervical length assessment are useful for prediction of PTL in high-risk cases.<sup>1</sup>

Role of salivary estriol and home uterine activity monitoring for prediction of preterm labor is not supported with enough evidence, hence both are not recommended in routine clinical practice.

### CAN WE PREVENT PTL?

Prediction of PTL even in high-risk women is difficult hence measures to prevent PTL has been attempted with tocolytics, antibiotics and progesterone.

**Antibiotics:** Studies have shown that use of antibiotics in the presence of abnormal vaginal flora or BV in early pregnancy has reduced the incidence of PTL but however other studies have conflicting reports. There is a wide variation in antibiotic selection and results are conflicting. However a randomized controlled trial with clindamycin as a single drug in early second trimester in cases with abnormal bacterial vaginal flora and BV had beneficial results.<sup>9</sup> However use of antibiotics in PPRM has reduced the incidence of neonatal morbidity but not preterm birth.<sup>10</sup>

**Progesterone:** Prophylactic use of 17 hydroxy caproate has significantly reduced the incidence of PTL but not useful in established PTL (From early pregnancy till 34 weeks).<sup>11</sup> Vaginal natural micronized progesterone is used for prophylaxis of PTL in women with short cervix with reasonable success.<sup>12</sup>

**Cervical Cerclage:** There is no clear evidence to support prophylactic cervical cerclage routinely. There may be beneficial effects with cerclage in women with short cervix. Role of emergency cervical cerclage is controversial; some have shown benefits of median prolongation of pregnancy by 4-5 weeks (1-18 weeks range) and survival rates upto 89%.<sup>13,14</sup> Use of emergency cerclage, indomethacin, antibiotics and bed rest have reduced PTL compared to antibiotics and bed rest alone.<sup>15</sup> However at present elective cerclage for prevention of PTL as routine is not recommended and before performing the emergency cerclage one should counsel with regard to the benefits and risks of the procedure (iatrogenic rupture of membranes and infection).<sup>1</sup>

## TREATMENT OR MANAGEMENT

As we do not know the cause of PTL accurately, prediction and prevention measures for PTL are met with little or no success. The treatment of PTL puts the obstetrician in clinical dilemma to use the measures with low success rate, lack of specific effects, some serious side effects (Betamimetics) and weak evidence of support for their use.

## TOCOLYTICS

These are drugs that relax the myometrium to inhibit uterine contractions. These agents act by different mechanisms and result in non availability of intracellular ionic calcium leading to inhibition of formation of actin-myosin complex. However, the usefulness of these agents is questioned. These produce serious maternal and fetal side effects. RCOG (2002) does not recommend their use as it is not supported with evidence.

However, these agents are of help to gain few days which will be beneficial, especially for the corticosteroids to act and also for *in utero* transfer to higher centre for better care.

The use of these agents after 34 weeks is not recommended and the lower gestational age limit is not clear.

These agents include:

1.  $\beta$ -sympathomimetics.
2. Calcium channel blockers.
3. Oxytocin receptor antagonists.
4. Prostaglandin synthetase inhibitors.
5. Magnesium sulphate.
6. Nitric oxide donors.

## $\beta$ -SYMPATHOMIMETICS

These include Isosuxprine hydrochloride, ritodrine, terbutaline and salbutamol. The use of these agents is associated with serious side effects like, arrhythmia (including tachycardia), hypotension, pulmonary edema, myocardial ischemia, and death.

Other less serious side effects are hyperglycemia and hypokalemia. These normally do not warrant any treatment unless the woman is diabetic or immediate surgery is contemplated.

Some tocolytics have specific side effects like, ritodrine may induce vasculitis in women with autoimmune disease, terbutaline may cause increased sensitivity (in babies who are exposed *in utero*) for abnormal neural effects to organo-phosphorous compounds if exposed in later life.<sup>16,17</sup> These drugs are no more recommended as their efficacy is inferior to calcium channel blockers and atosiban.

## CALCIUM CHANNEL BLOCKERS

These (Nifedipine and nicardipine) are the first choice agents for tocolysis. These drugs can be used even in women with twin pregnancy, diabetes mellitus, heart disease including cardiomyopathy, where other agents are contraindicated. These agents do not have significant effects on hemodynamic and metabolic changes.<sup>18,19</sup> These agents are superior to atosiban

(an oxytocin receptor antagonist) in effectiveness and are much cheaper than it.<sup>20</sup> Side effects like myocardial infarction and deaths have been noted rarely with use of nifedipine especially in woman with cardiovascular diseases.<sup>21,22</sup>

## Atosiban

An oxytocin receptor antagonist useful in preterm labor. However it is less effective and costlier compared to calcium channel blockers, but with fewer side effects like chest pain, palpitations, tachycardia, hypotension, nausea, vomiting and headache.<sup>20,23</sup>

## Prostaglandin Synthetase Inhibitors

Drugs like indomethacin are being used in the treatment of PTL. The use of these agents is associated with potential fetal risks like premature closure of ductus arteriosus, persistent pulmonary hypertension, renal and cerebral vasoconstriction and necrotizing enterocolitis and prolonged renal insufficiency in the preterm infant specially in higher doses (>200 mg /day and for > 48 hours).<sup>24,25</sup> Other agents like selective cyclo-oxygenase 2 inhibitors are under trial.

## Magnesium Sulphate

Magnesium sulphate as a tocolytic is no more recommended as its use has been associated with increased mortality for the newborn and its ineffectiveness to prevent/delay the preterm birth.<sup>26</sup>

## Nitric Oxide Donors

There is insufficient evidence to support the use of nitric oxide donors (nitroglycerine) in preterm labor.<sup>27</sup>

**Maintenance of tocolytic therapy** is attempted with varying success with no improvement in the recurrence episodes of PTL and perinatal outcome.<sup>28</sup>

## Corticosteroids

Use of antenatal (24-34 weeks) corticosteroids is associated with reduction of respiratory distress syndrome, neonatal death, intraventricular hemorrhage and necrotizing enterocolitis (betamethasone).<sup>29</sup> Single course of therapy is recommended.<sup>29</sup>

**Newer developments:** Research is underway in identifying the cause for preterm labor with special reference to infection with various agents that leads to separation of membranes as a consequence of infection. Search for selective and safe tocolytic is also under consideration, specially the prostaglandin synthetase inhibitors and the role of potassium channels in myometrium.

## CONCLUSION

Successful prediction, prevention and treatment of preterm labor has significant influence on the perinatal outcome, health care

expenditure and quality of life. As the cause for preterm labor is still an enigma, it is difficult to predict, prevent or treat PTL successfully. At present the treatment of PTL is mainly antibiotics, tocolytics and corticosteroids with varied success. The goal of treatment of preterm labor should be to improve perinatal outcome and reduce morbidity and mortality.

## ACKNOWLEDGMENTS

We acknowledge efforts of Mr. Malleshi Naik, Staff member, Perinatal Center, JN Medical College, Belgaum.

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