Recent advances in management of preterm labor

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Introduction
Preterm labor refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of cervix between 20 and 37 weeks of gestation. Preterm labor complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide. It is a major public health problem in terms of loss of life, long-term disability (cerebral palsy, blindness, deafness, chronic lung disease) and health care costs both in the developing and the developed world. In the USA, approximately 450,000 (11.5%) preterm births occur annually, directly contributing to 75% of neonatal mortality and 50% of long-term neurological impairment in children. Moreover, it accounts for 35% and 10% of healthcare spending for infants and children, respectively. Many developing countries are unable to cope with the healthcare costs associated with managing neonates that are born preterm, resulting in higher and often unacceptable neonatal morbidity and mortality.

Unfortunately, the incidence of preterm labor has changed very little over the last 40 years and uncertainties still persist regarding the best strategies for its management. It has been widely recognised that its prevention and/or effective management will improve neonatal outcome and will have a profound impact on societal and long-term public healthcare costs. In this article we review the epidemiology and recent advances in prediction, prevention and management of preterm labor.

Epidemiology of preterm labor
Overall incidence of preterm labor is reported to be 6-15% and 4-50% of these occur spontaneously, whereas 25% occur following preterm pre-labor rupture of membranes (PPROM). Iatrogenic preterm labor due to obstetric intervention to avoid maternal or fetal compromise, accounts for about 25%.

Prediction of preterm labor
Up to 75% of preterm labor occurs either spontaneously or following PPROM and many attempts have been made to develop methods that may help us to predict the onset of preterm labor so that measures could be taken to prevent its occurrence. These include –

1. Risk markers
2. Home uterine activity monitoring (HUAM)
3. Salivary estriol
4. Screening for bacterial vaginosis (BV)
5. Screening for fetal fibronectin (fFN)
6. Cervical ultrasonography (cervical length assessment)

Risk markers
A previous history of preterm labor is the strongest risk marker. It has been estimated that the incidence of preterm labor in subsequent pregnancies after one preterm birth rises to 14.3% and after two preterm births to 28%.

Other risk markers include multiple pregnancy, cigarette smoking, cervical incompetence or uterine anomalies, uterine over-distension (polyhydraminos, macrosomia, fibroids), previous cervical surgery, using smokeless tobacco, bleeding in early pregnancy, bacterial vaginosis, poor socio-economic or educational status, and young or advanced maternal age. Pre-conceptional multivitamin treatment was inversely associated with both early and late preterm birth. There is now evidence to support an association between severe periodontal disease and spontaneous preterm labor. Short interval between pregnancies (less than 12 months) has been found to increase the risk of recurrent preterm birth. Recently, domestic violence, especially injury due to physical abuse, was found to be significantly associated with both preterm birth and low birth weight. Unfortunately,
most of these risk markers are poor predictors of preterm labor as they have variable sensitivities (35-60%) and positive predictive values (15-30%) 11.

**Home uterine activity monitoring (HUAM)**

HUAM is based on the principle of tocodynamometry and created a lot of interest and excitement among obstetricians when it was first introduced. It was tried in women with risk markers for preterm labor. The technic involves telemetric recording of uterine contractions and transmission of the same to a monitoring center and daily feed back from the healthcare practitioner to offer patient support and advice. Earlier studies showed that HUAM was effective in predicting the onset of preterm labor, but they were criticized for their flawed study design. To date about 13 randomized trials have been done of HUAM and the results are inconclusive. Recently, a large randomized trial involving 2422 patients showed no benefit of HUAM in predicting preterm labor 12. Hence, it cannot be recommended in routine clinical practice.

**Salivary estriol**

Studies on the physiology of parturition in sheep have demonstrated the role of fetal hypothalamo-pituitary-adrenal (HPA) axis and the resultant increase in the production of estriol from the placenta at the onset of labor. Extrapolated to the human pregnancy, premature activation of HPA axis in preterm labor may increase the serum and salivary levels of estriol in the mother and this may predict the onset of preterm labor early. Two prospective trials showed that salivary estriol was more effective in predicting preterm labor than traditional risk assessment 13. However, this test has very poor sensitivity and specificity and has a very high false positive rate, which may increase the cost of prenatal care due to unnecessary intervention. There is a diurnal variation of the maternal salivary estriol level and it has been reported that administration of betamethasone to effect surfactant production may suppress maternal salivary estriol levels 14. Both these factors may pose difficulties in interpretation of the results.

**Screening for fetal fibronectin (fFN)**

Fetal fibronectin (fFN) is a basement membrane protein produced by the fetal membranes and functions as an ‘adhesion binder’. It facilitates the attachment of the placenta and membranes to the uterine decidua and is normally detectable in cervical secretions until 16-20 weeks of gestation. Appearance of fFN in cervical secretions after 24 weeks of gestation may indicate disruption of the normal adhesion between chorioamnion and the underlying decidua. Hence, it may be a marker of inflammation of the fetal membrane / decidual inter-phase, with or without infection, that often heralds the onset of preterm labor. Many studies have shown an increased risk of preterm birth, if fFN is positive after 24 weeks and decreased risk if this protein is negative in cervical secretion. A meta-analysis of 40 studies revealed a very high negative predictive value for fFN in predicting the onset of preterm birth in the next 3 weeks 21.

The specificity of fFN test for predicting preterm delivery within 1 and 2 weeks was 89%, whereas for delivery within 3 weeks it was 92%. The sensitivity of the test in predicting the onset of preterm labor within 1 week and 3 weeks was 71% and 59%, respectively 21.

It appears that a negative fFN test is useful in ruling out an imminent preterm delivery, whereas the implication of a positive test is uncertain. It can be recommended in high-risk women who fulfill the criteria of intact membranes, minimal cervical dilatation (<3 cm), and gestation between 24-34 weeks. Most importantly, the results should be made available within a time frame that allows for clinical decision-making (usually 24 hours).

**Cervical ultrasonography (cervical length assessment)**

Cervix plays a dual role in pregnancy. It maintains the uterine contents against the effects of gravity and intrauterine pressure until labor and dilates to allow the passage of these contents
during delivery. Cervical competency depends on the anatomical integrity as well as the biochemical composition (ground substance) of the cervix. One of the earliest indicators of cervical incompetency or onset of labor is shortening of the cervix. Interest in the assessment of cervical length using ultrasound as a predictor of preterm labor arose after Iams et al \(^2\) established the normal distribution of cervical lengths after 22 weeks of gestation. It is widely accepted that a cervical length of less than 25 mm between 24-28 weeks may increase the relative risk of preterm delivery. A prospective trial involving 2915 women evaluated by serial cervical ultrasonography reported a relative risk of preterm delivery of 9.57, 13.88 and 24.94 for cervical lengths of < 26 mm, < 22 mm and < 13 mm, respectively at 28 weeks of gestation. The results of various studies using cervical length assessment as a predictor of preterm delivery were not always reliable or reproducible. There is also a wide variation in predictive values. A systemic review of 35 studies involving cervical length assessment revealed a very wide variation in sensitivity (68-100\%) and specificity (44-79\%) \(^3\). Hence, currently there is no strong evidence to support routine cervical assessment using ultrasound between 24-28 weeks for the purpose of predicting preterm delivery. However, it may have a place in high-risk pregnancies or in combination with fFN assessment.

**Combination of fFN and cervical ultrasonography**

Cervical length assessment in conjunction with fFN estimation in cervicovaginal secretions in women with high risk of preterm delivery may be useful. A study to determine the risk of recurrence of spontaneous preterm delivery in women with prior preterm birth reported a risk of 65\% if the cervical length is less than 25 mm and the fFN is positive.\(^4\) However, if the fFN is negative, the risk of preterm delivery was only 25\%. As shown in Table 1, the risk of recurrent preterm delivery in women with cervical length > 35 mm and negative fFN was only 7\%. Hence, a combination of cervical length assessment using ultrasound scan and estimation of fFN may help predict the recurrence of preterm delivery in high-risk women.

**Table 1. Combination of cervical length assessment and fetal fibronectin fFN in predicting recurrent risk of preterm delivery.**

<table>
<thead>
<tr>
<th>Cervical length</th>
<th>Recurrent risk of preterm delivery</th>
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<tbody>
<tr>
<td></td>
<td>fFN Positive</td>
</tr>
<tr>
<td>&lt; 25 mm</td>
<td>65%</td>
</tr>
<tr>
<td>26 – 25 mm</td>
<td>45%</td>
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<tr>
<td>&gt; 35 mm</td>
<td>25%</td>
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**Prevention of preterm delivery**

It is quite clear that although many methods have been employed to predict preterm delivery, there is very little success even in high-risk women. This has resulted in developing measures to prevent preterm labor in high-risk women and these include use of tocolytic drugs, antibiotics and hormones (progesterone). Role of antibiotics has been controversial. A recent randomised controlled trial concluded that treatment of asymptomatic abnormal vaginal flora and BV with oral clindamycin in early second trimester significantly reduces the rate of late miscarriage and spontaneous preterm birth.\(^5\) Other studies have reported conflicting results and there is wide variation in patient selection as well as the antibiotics used. However, there is evidence from ORACLE Trial that the use of antibiotics in patients with preterm pre-labor rupture of membranes (PPROM) reduces neonatal morbidity, although there is no reduction in the incidence of preterm birth.\(^6\) Therefore, it appears that use of antibiotics may reduce the neonatal complications without having any effect on the incidence of preterm births in patients with PPROM. A recent Cochrane Review concluded that there is no overall benefit from prophylactic antibiotics in preterm labor with intact membranes on neonatal outcome.\(^7\)

A recent multi-centre randomized controlled trial concluded that prophylactic use of 17-hydroxy progesterone caproate significantly reduced the incidence of preterm labor.\(^8\) It was not useful in suppressing established (active) preterm labor. Further studies are needed to confirm these findings and to determine the dosage, timing of commencement and duration of treatment with progesterone.

Cervical cerclage has been tried to prevent preterm delivery in women with ultrasonographic evidence of short cervix. A recent survey among the obstetricians found a significant uncertainty surrounding the decision whether to place a cerclage and there is a considerable variation in the clinical practice on its placement.\(^9\) A very recent multi-center randomized controlled trial using cervical length of 15 mm as a cut-off point concluded that use of Shirodkar suture in women with short cervix does not substantially reduce the risk of early preterm delivery.\(^10\) However, this study did confirm that routine sonographic measurement of cervical length at 22-24 weeks identifies a group at high risk (22\% in cerclage group vs 26\% in control group) of early preterm births (before 33 weeks). The effectiveness of emergency cerclage in women with bulging membranes to prevent an impending preterm birth is even more controversial. Fetal survival rates of up to 89\% have been reported.\(^11\) Some studies reported a median duration of prolongation of pregnancy of 4.5 weeks (range 1 day to 18 weeks) after this procedure.\(^12\) Recently, cervical incompetence prevention...
randomized cerclage trial concluded that emergency cerclage, indomethacin, antibiotics and bed rest reduced preterm delivery before 34 weeks compared to bed rest and antibiotics alone. In the light of current evidence, elective cervical cerclage for the prevention of preterm labor in routine obstetric practice cannot be recommended as its effectiveness has been questioned by a recent randomized trial. There is insufficient evidence to support the use of emergency cerclage in women with bulging membranes and women should be counseled regarding the procedure and risks including iatrogenic rupture of membranes and infection.

Treatment of preterm labor

Lack of reliable and effective methods to predict or prevent preterm labor has resulted in very little change in the incidence of preterm deliveries over the last 40 years. Clinicians are often faced with the dilemma of managing an established preterm labor with a variety of pharmacological agents, which may have a lack of utero-specificity, low efficacy or potentially serious side effects for the mother or the fetus. Scientific evidence supporting the use of some of these treatment modalities is not very strong. The measures that are commonly used are tocolytic drugs, corticosteroids and antibiotics.

Tocolytics

These are pharmacological agents that relax the uterine myometrium and inhibit uterine contractions leading to abolition of preterm labor. They act through a variety of mechanisms to decrease the availability of intracellular calcium ions leading to inhibition of actin-myosin interaction. Their effectiveness in suppression of preterm labor has been controversial and many of these agents are associated with serious side effects to both mother and her fetus. The Royal College of Obstetricians and Gynecologists (RCOG), in their evidence-based guideline on preterm labor recommend that it is reasonable not to use tocolytic drugs, as there is no clear evidence that they improve outcome. However, tocolytics should be considered if the few days gained would be put to good use such as completing a course of corticosteroids or in-utero transfer. They are not recommended after 34 weeks of gestation and currently there is no consensus regarding the lower gestational limit at which they could be used.

Betasympathomimetic drugs

Ritodrine, terbutaline and salbutamol are the commonly used betasymptoms drugs that act through c-GMP to inhibit uterine contractions. They are associated with serious maternal (pulmonary edema, myocardial ischemia, arrhythmia and death) side effects. Although, hyperglycemia and hypokalemia are recognised complications, there is no need to administer insulin for hyperglycemia and potassium for hypokalemia unless the patient is a known diabetic or requires immediate surgery. In pregnant women with autoimmune disease, ritodrine should be used with caution because it may induce vasculitis. There are also concerns that terbutaline may act as a developmental neurotoxicant and in-utero exposure to it may create a subpopulation that is sensitized to adverse neural effects of a subsequent exposure to organophosphorous insecticides. A large multicenter study comparing these three beta-agonists with oxytocin antagonist (atobisban) concluded that there was little difference in their effectiveness in delaying delivery between these groups. However, atosiban was associated with fewer maternal side effects. The RCOG recommends that if a tocolytic drug is used, ritodrine is no longer first choice. Atosiban and nifedipine appear to be preferable as they have fewer adverse effects and seem to have comparable effectiveness.

Calcium channel blockers

Interest in calcium channel blockers arose to reduce the cardiovascular complications of beta-agonists. Use of nifedipine in preterm labor was associated with a lower incidence of adverse hemodynamic and metabolic changes compared to ritodrine after 24 and 48 hours of tocolysis. Nifedipine and nicardepine have been used in this regard and they are especially useful in women with twin pregnancy, diabetes mellitus, heart disease and cardiomyopathies, all of which are adversely affected by beta-agonists. A systemic review of 12 randomized controlled trials concluded that calcium channel blockers (nifedipine) are safer and more effective than betamimetics. Nicardepine was also found to be more effective and safer than salbutamol in another prospective randomized controlled trial. A recent Cochrane Review on preterm labor concluded that when tocolysis is indicated for preterm labor, calcium channel blockers are preferable to other tocolytic agents especially compared with betamimetics. They have been shown to reduce the number of women delivering within the next 7 days and the incidence of respiratory distress syndrome (RDS), necrotising enterocolitis, intraventricular hemorrhage and neonatal jaundice. A recommendation has been made by the Royal College of Obstetricians and Gynecologists (RCOG) to use nifedipine (or atosiban) as the first line treatment in preference to betamimetics. However, a recent meta-analysis concluded that when indirectly compared (delay in delivery by 48 hours and reduction in RDS) to atosiban, nifedipine tocolysis is more effective. Commonly used regimen is 20 mg initial dose followed by 10-20 mg every 4-6 hours until the uterine contractions subside, and in-utero transfer and/or steroid administration was completed. Though rare, serious side effects including myocardial infarction and deaths have been reported with the use of nifedipine, especially in women with cardiovascular disorders. Limited data is available regarding the use and safety of nicardepine in preterm labor.
Recently, Vaast et al 48 reported five cases of acute pulmonary edema with nicardipine therapy for preterm labor.

**Atosiban**

There is sufficient evidence to suggest that atosiban is equally effective as betamimetics in delaying preterm labor and is associated with fewer side effects including chest pain, palpitations, tachycardia, hypotension, nausea, vomiting and headache 39. Although, it is recommended by the RCOG along with nifedipine as a first line agent in the management of preterm labor, its cost may preclude its use in developing countries.

**Prostaglandin synthetase inhibitors**

Indomethacin is the cyclo-oxygenase inhibitor that is used in the treatment of preterm labor. Although it has fewer maternal side effects, it is associated with potential fetal risks including premature closure of ductus arteriosus with persistent pulmonary hypertension, renal and cerebral vasoconstriction and necrotising enterocolitis 34. A recent 5-year retrospective study concluded that antenatal indomethacin could result in significant prolonged renal insufficiency in the preterm infant 49. These side effects are more likely seen with higher dosage and prolonged treatment. It may be advisable to limit treatment for less than 48 hours and not to exceed 200 mg/day. Currently, in the light of these adverse and potentially serious fetal side effects, it may only be used as a second line agent in early gestational age preterm labor 34. There may be a place to use this as a first line agent in preterm labor secondary to polyhydraminos as it may reduce the formation of amniotic fluid. However, evidence for this is lacking. Celecoxib, a selective cyclo-oxygenase 2 inhibitor has also been tried in the treatment of preterm labor. A recent prospective randomized controlled trial comparing celecoxib with indomethacin concluded that celecoxib has a better safety profile than indomethacin 50. Further trials are needed to assess its safety profile and efficacy before it can be recommended for routine clinical practice.

**Other tocolytic agents**

There is no evidence to support the use of magnesium sulphate in the treatment of preterm labor. A Cochrane Review has concluded that magnesium sulphate is ineffective in delaying preterm birth or preventing preterm birth and its use is associated with increased mortality for the infant 51. However, no potentially serious maternal side effects like respiratory depression or arrest have been observed 52.

Nitric oxide donors have been found to be potent uterine relaxants in vitro 53 and transdermal nitroglycerine has been reported to be safe for the mother and the fetus 54. A recent Cochrane Database of Systemic Reviews included five randomized trials involving nitric oxide donors (nitroglycerine). Nitric oxide donors did not delay delivery or improve neonatal outcome when compared to placebo, no treatment or other tocolytics. Although, the side effect profile was better than that with other tocolytics, more women experienced headaches. It concluded that currently there is insufficient evidence to support routine administration of nitric oxide donors in the treatment of threatened preterm labor 55.

**Maintenance of tocolysis**

There is currently no evidence to support maintenance therapy with tocolytic drugs. Terbutaline pump maintenance therapy has not been shown to decrease the risk of preterm labor by prolonging pregnancy 56. The benefits of maintenance therapy with calcium channel blockers are still unclear 57, although it has been reported that the gestational age and time gained from initiation of maintenance therapy to delivery were longer in women receiving oral maintenance tocolysis with nifedipine 58. There was however no decrease in the recurrence of preterm labor episodes or improvement in the perinatal outcome.

**Corticosteroids**

There is evidence that antenatal corticosteroids are associated with a significant reduction in the rates of respiratory distress syndrome, neonatal deaths and intraventricular hemorrhage, although the numbers needed to treat increase significantly after 34 weeks 59. The RCOG has recommended that antenatal corticosteroids should be administered between 24 and 34 weeks of gestation. Betamethasone appears to reduce the incidence of necrotising enterocolitis as compared to dexamethasone. The optimum treatment-delivery interval for administration of antenatal corticosteroids is after 24 hours and within 7 days of administration 59. A survey of UK obstetricians conducted in 1997 reported that 98% of responders prescribed repeated courses of antenatal corticosteroids 60. One randomized controlled trial of single versus multiple courses of corticosteroids involving 502 pregnant women between 24 and 32 weeks of gestation concluded that weekly courses of antenatal corticosteroids did not reduce composite neonatal morbidity compared to single course of treatment 61. The RCOG guideline on antenatal corticosteroids has concluded that currently there is no evidence to recommend multiple courses of antenatal corticosteroids 59. A recent 2 year follow up study after single or multiple antenatal courses of corticosteroids found an association of multiple courses of dexamethasone (not betamethasone) with an increased risk of leukomalacia and 2 year infant neuro-developmental abnormalities 62.

**Conclusion**

Prevention and treatment of preterm labor is essential to reduce adverse neonatal and infant outcome and to improve
survival and quality of life. Such an approach will have a great impact on societal and long term public health-care costs. Unfortunately, an ideal tocolytic drug that is uterine-specific with minimal maternal and fetal side effects and that significantly improves neonatal outcome still eludes us. At the Canadian Tocolysis Consensus Conference it was concluded that there is little evidence to support the use of any of the currently available tocolytics and that tocolytic use has not been associated with improved perinatal outcomes and often has detrimental effects on the mother. There is still much confusion regarding the ideal tocolytic and this has been exemplified by a recent survey among the obstetricians in Australia and New Zealand, which revealed a wide range of opinions and uncertainty over the effectiveness of tocolytic therapy in clinical management, the most appropriate drug and side effects.

Future research is needed on cyclo-oxygenase selective prostaglandin inhibitors, the use of multiple drugs with more utero-selectivity and fewer side effects, and the development of oxytocin antagonists with better efficacy. Prostaglandin F2 alpha receptor antagonists should also be explored. Research is also needed to develop technics to effectively predict preterm labor. Mannan Binding Protein (MBP) is homologous to surfactant protein and is found in fetal membranes. There is a suggestion that a deficiency of this protein may be used as a predictor of preterm births and further research is needed to confirm this hypothesis. Recently, the role of potassium channels in human myometrium has been analysed and down regulation of betasubunits of calcium-activated potassium channel in human myometrium during preterm labor has been demonstrated. These findings may generate future research into the development of potassium channel modulators to arrest preterm labor. The ultimate goal of management of preterm labor should not be to merely prolong pregnancy but to improve neonatal outcome and to reduce morbidity and mortality.

References