Preterm delivery: current concepts

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Introduction

Preterm delivery (PTD) occurs in approx 13 million women, representing almost 10% of total births worldwide and is the leading cause of perinatal morbidity and mortality in the world[1]. All births before 37 weeks' gestation are defined as preterm but the vast majority of morbidity and mortality relates to early delivery before 34 weeks, which occurs in 2% of pregnancies[2]. Extreme PTD (< 28 weeks) and early PTD (28-30 weeks), each occurring in about 0.25% of pregnancies, moderate PTD (31-33 weeks) occurring in about 0.6% of pregnancies and mild PTD (34-36 weeks) occurring in about 3.0% of pregnancies constitute the balance PTD[2]. The burden of PTD is disproportionately distributed with approximately 54% of PTD occurring in Asia and another 31% PTD occurring in Africa. In comparison, around 7.5% of PTD occur in Europe and North America together[1].

The morbidity, mortality and costs of PTD are higher at lower gestational ages with mortality rates of approximately 90% at 23 weeks decreasing to 2% at 34 weeks. Even in babies that survive there is a higher risk of short term and long-term morbidity[2]. Some associated conditions are acute and amenable to treatment but others such as cerebral palsy, neurodevelopmental and pulmonary disorders can result in long-term, severe disability[3].

This review will not address the issues related to iatrogenic PTD (eg. PTD due to pre eclampsia, fetal growth restriction etc).

Aetiology

Approximately 70-80 percent of PTD occur spontaneously as a result of preterm labour (PTL - 45-50%) or preterm prelabour rupture of membranes (PPROM – 30%). Iatrogenic PTD for maternal or fetal problems contributes to the remaining 20-25%[1].

Clinical and laboratory evidence suggest that a number of pathogenic processes can lead to a final common pathway that results in spontaneous PTD.

The four primary processes are:

- Premature activation of the maternal or fetal hypothalamic-pituitary-adrenal axis.
- Exaggerated inflammatory response/infection.
- Decidual hemorrhage.
- Uterine over distension. (eg multiple pregnancy or polyhydramnios)

These processes may be initiated long before PTL or PPROM is diagnosed clinically. Another cause for PTD is cervical weakness either congenital or as a result of previous cervical surgeries.

Screening and prediction of pre term labour

Many different approaches have been suggested for the screening and prediction of PTL. Many such primary predictors of PTL eg. Papiernik-Creasy score[4] and Berkowitz's score[5] have been proposed to estimate the baseline risk of PTD. Unfortunately the predictive value of these scores, especially their specificity, is poor mainly because all the risk factors are indirect factors.

Secondary predictors (based on examinations done during the index pregnancy) allow a more accurate assessment of the risk of PTD in individual women. Detection of fetal fibronectin (fFN) from cervicovaginal secretions and cervical shortening diagnosed by transvaginal ultrasonography have emerged as the major secondary predictors of PTD[3,6]. fFN is a basement membrane protein which is produced by the fetal membranes. It is an adhesion binder of the placenta and membranes to the deciduas and is normally present in cervical secretions until 16-20 weeks. It can be used as a marker for the disruption of the chorio-amnion and underlying decicua, due to inflammation with or without infection. A positive fFN test in the midtrimester of pregnancy is associated with early spontaneous PTD. However most women will not deliver following a positive test, indicating a low positive predictive value. In contrast, fFN has a very high negative predictive value, and the chance of delivering within the next 7 days is extremely low when fFN is negative[6].

In a prospective population based multicentre study carried out in 39,284 women with singleton pregnancies, the cervical length, measured by Trans Vaginal Ultrasound Scan (TVUSS) at 22-24 weeks was normally distributed with a mean of 36 mm. The cervical length at this same gestational age was ≤15 mm in approx. 1% of women. The probability of spontaneous PTD was influenced by maternal age and obstetric history and was inversely related to cervical length. The detection rate of spontaneous PTD before 32 weeks, for a fixed false-positive rate of 5%, when screening by maternal factors alone, cervical length alone and by the combination of maternal factors and

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cervical length was 29%, 48% and 57%, respectively. The respective values for a fixed false-positive rate of 10% were 38%, 55% and 69% respectively[7].

Both markers (cervical length and fFN) have been extensively studied and have been consistently shown to be strong, short term predictors of preterm birth across a wide range of gestational ages.

There are other secondary predictors of PTL which have been found to be useful. One such marker is salivary estriol. The presence of salivary estriol is associated with late PTD[8]. This is in contrast, to a positive fFN test in the midtrimester of pregnancy which is associated with early PTD. As both tests have low test sensitivity and positive predictive value they are currently used clinically for their negative predictive values[9]. Another marker with high negative predictive value as fFN is the non detection of phosphorylated insulin-like growth factor binding protein-1 in cervical secretions[9].

The association between bacterial vaginosis (BV) and PTD has been the subject of a large number of case-control and prospective cohort studies. A recent meta-analysis of 18 studies involving 20,232 women showed that BV doubles the risk of PTD at less than 37 weeks of gestation (odds ratio 2.19; 95% CI 1.54-3.12). A subgroup analysis of the included studies suggested that the risk of PTD birth is further increased by 5-times when the diagnosis of BV is made early in pregnancy (<16 weeks)[10]. Antibiotic treatment can eradicate BV in pregnancy but the effectiveness of treatment of BV in pregnancy in reducing PTD is not clear.

As all the above mentioned secondary predictors have high negative predictive values and low positive predictive values, many other biochemical markers are being studied. This is with the aim of developing a prediction model to identify those at greatest risk of having PTD among women who have PTL. These biochemical markers are: increased level of nitric oxide metabolites and corticotrophin releasing hormone in serum, increased lactoferrin concentration in cervical secretion, increased tumor necrosis factor-alpha, serum Interleukin-6 and high matrix metalloproteinase-8 concentration in amniotic fluid, and the presence of Ureaplasma urealyticum in amniotic fluid[11,12,13]. As the sensitivity and positive predictive value of a single marker in predicting PTD is only moderate, serial examination of markers, combination of different markers and multiple markers have all been studied and have shown limited results. However a recent cohort study using a combination of maternal serum proteins and cervical length as a prediction model for PTD in women with threatened PTL has shown promising results[14].

The Cervical Resistance Index (CRI) is a diagnostic test described to detect cervical weakness. However, there is insufficient evidence to recommend the use of prepregnancy diagnostic techniques such as CRI, hysterography or insertion of cervical dilators aimed at diagnosing 'cervical weakness' in women with a history of PTD and/or second-trimester miscarriage, to assist in the decision to carry out a history-indicated cervical cerclage.

The value of women using home uterine monitoring in the early detection and management of PTL and the implications of this techniques for organization of delivery of care are unclear[15].

Prevention of preterm labour

The effectiveness of different interventions to prevent PTL varies among different categories of women. Three main categories have been identified to assist the conduct of meaningful clinical trials, and also help the clinician to choose the most appropriate method of preventing PTL. These categories are: i) low risk women without a previous history of PTL but having an ultrasonically detected short cervix at 22-24 weeks gestation ii) high risk women with a previous history of PTL iii) women with multiple pregnancies.

Another special category of women are those who have an uterine abnormality or have had previous cervical surgery. This latter category will not be discussed in this review.

Low risk women without a previous history of preterm labour but having an ultrasonically detected short cervix at 22-24 weeks gestation

In women with a short cervix of ≤15 mm diagnosed by routine TVUSS at 22-24 weeks gestation, two strategies can be attempted to reduce the risk of PTD. The first is administration of progesterone. Progesterone can be administered orally, vaginally and intramuscularly. Oral micronized progesterone has been found to be effective in reducing preterm birth in several studies[16,17]. Vaginal administration of progesterone 200 mg per night from 24 to 34 weeks can reduce the rate of spontaneous PTD before 34 weeks by about 45%[18] and is associated with a reduction of composite perinatal morbidity and mortality[19-21]. This method is increasingly favoured because natural formulation of progesterone is administered vaginally and it can lead higher endometrial concentrations compared to oral or intramuscular administration. However several unanswered questions still remains regarding the formulation, optimal dose, route and frequency of administration of progestins for prevention of PTL. Currently 250mg of the synthetic progestagen 17-alpha-hydroxy-progesterone caproate (17-OHP-C) is the only US Food and Drugs Administration approved formulation of progestin for prevention of preterm birth, although there is significant controversy surrounding its cost[22,23]. Additionally, there is some concern that injections of 17-OHP-C may increase the risk of fetal death[24].

The second strategy is performing a cervical cerclage in singleton pregnancies with a short cervix and no previous history of PTD. However this reduces the risk of spontaneous PTD before 34 weeks by only 15%[25]. Therefore, vaginal progesterone is the method of choice and cervical cerclage

is not routinely recommended in this category of women. Although universal screening of cervical length in women without a PTD is not mandatory[19,21], this screening strategy may be considered if facilities are available. The cost effectiveness of universal screening in low risk women and treating the mothers with progesterone when the cervix is short is currently being studied[26].

The insertion of an ultrasound-indicated cerclarge is not recommended in women without a history of spontaneous PTD or second-trimester loss who have an incidentally identified short cervix of 25 mm or less[25].

The use of a cervical pessary could prevent PTD in a population of appropriately selected at-risk women previously detected to have a short cervix at the mid trimester scan[27].

Prevention of preterm labour in high risk women with a previous history of preterm labour

Resting in bed in a hospital or at home was previously recommended for the prevention of PTD but there is no scientific evidence to support this practice[28]. Betamimetics given prophylactically do not prevent PTD[29]. There is also no evidence to suggest that life style interventions, such as decrease in manual labor, increased visits to antenatal clinics, psychological support, or diet supplementation with iron, folate, calcium, zinc magnesium, vitamins, or fish oil reduce the risk of PTD[30].

A history-indicated cerclage should be routinely offered only to women with three or more previous PTD and/or second-trimester losses[31,32]. Cervical cerclage reduces the risk of delivery before 34 weeks by about 25% in these groups. There are two options in the management of patients with previous PTD. Firstly, elective cerclage in all women soon after the 11-13 weeks scan demonstrates no major fetal abnormality. Secondly, measurement of cervical length every two weeks and placement of a suture only if cervical length becomes <25 mm. The overall rate of PTD is similar with the two approaches but the second approach is preferable because it reduces the need for cerclage by about 50%[31]. Progesterone given from 20 to 34 weeks reduces the risk of PTD before 34 weeks by about 25%. Natural progesterone vaginally is preferable because of lack of undesirable side effects, such as sleepiness, fatigue and headaches.

Multiple pregnancy

Progesterone treatment does not reduce the incidence of PTD in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent PTD in women with multiple gestations[21,33-,35].

A meta-analysis of trials on twin pregnancies with a short cervix (<25 mm) has also shown that cervical cerclage could increase the risk of PTD and that prophylactic administration of progesterone does not reduce the risk of PTD[35].

The insertion of a history- or ultrasound-indicated cerclage in women with multiple pregnancies is also not recommended, as there is some evidence to suggest it may in fact be detrimental. It has been associated with an increase in PTD and pregnancy loss[25].

Management of pre term labour

A careful history and speculum examination to diagnose PTL should not be overlooked as the diagnosis remains clinical in most instances. Digital vaginal examination should be avoided, especially if there is any suggestion of ruptured membranes as this increases the risk of ascending infections. The diagnosis should be based on regular uterine contractions occurring with a frequency of at least one every 10 minutes and either ruptured membranes or evidence of progressive cervical change on repeat vaginal examinations.

A urine full report, urine for culture and antibiotic sensitivity, high vaginal and endocervical swab for culture (including Chlamydia) and antibiotic sensitivity should be carried out. An ultrasound examination should be carried out to check the presentation, estimated fetal weight and liquor volume, and umbilical artery Doppler studies.

If ≥ 34 weeks gestation and a neonatal intensive care (NICU) cot is available, labour should be allowed to progress with continuous fetal heart rate monitoring. If <34 weeks gestation and a NICU cot is not available, an *in utero* transfer to a centre with NICU facilities should be considered. If >34 weeks gestation and no NICU facilities are available the decision to manage the woman or transfer to another hospital would depend on the neonatologist and the consensus opinion of the woman and her partner.

Corticosteroid therapy

If the gestation is between 24 and 35 weeks a single course of antenatal corticosteroids should be given[36]. Antenatal corticosteroids are most effective in reducing Respiratory Distress Syndrome (RDS) in neonates being delivered 24 hours after and up to 7 days after completion of corticosteroid therapy. Antenatal corticosteroids use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time period[37]. In low resource settings, Dexamethasone 6 mg given intramuscularly, 12 hrly for four doses is preferable to the more expensive Betamethasone 12 mg given intramuscularly daily for two days, as both regimens are equally effective[38-40]. Antenatal corticosteroids are effective not only in reducing RDS but also in reducing other complications of prematurity such as intraventricular haemorrhage[37].

Tocolytic therapy

Tocolytic therapy of an acute episode of idiopathic PTL often abolishes contractions temporarily, but does not remove the underlying stimulus

that initiated the process of parturition or reverse parturitional changes in the uterus. Further, there is no clear evidence that the use of a tocolytic drug is associated with a reduction in perinatal or neonatal mortality, or neonatal morbidity. However, tocolysis should be considered if the few days gained could be put to good use, such as completing a course of corticosteroids or affecting an in utero transfer. There is insufficient evidence for any firm conclusions to be made about whether or not tocolysis leads to any benefit in preterm labour in multiple pregnancy.

Nifedipine and atosiban have comparable effectiveness in delaying delivery for up to seven days[41,42]. Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data available[41]. Beta-agonists have a high frequency of adverse effects compared to nifedipine, atosiban and the cyclooxygenase inhibitors[43,44]. Using multiple tocolytic drugs appears to be associated with a higher risk of adverse effects and therefore should be avoided[45].

The dosage of nifedepine used in clinical trials varied from 30 mg/day to 160 mg/day until uterine contractions stopped[41]. The largest trial used nifedepine 10 mg sublingually, repeated if necessary per orally 10mg every 15 minutes up to 40 mg in the first hour. The maintenance dose was 60-160 mg/day up to 34 weeks[46]. The suggested dose of nifedipine by the Royal College of Obstetricians and Gynaecologists is an initial oral dose of 20 mg followed by 10-20 mg three to four times daily, adjusted according to uterine activity for up to 48 hours[47]. A total dose above 60 mg appears to be associated with a three- to four-fold increase in adverse events[48]. A suggested dose of atosiban of an initial bolus dose of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours (upto a maximum of 330 mg)[47].

Another useful tocolytic agent is Glyceryl Trinitrate (GTN) - a nitric oxide donor. Nitric oxide is a potent muscle relaxant and therefore is a good tocolytic agent. In the uterine cervix however it has a completely different action and causes cervical ripening[49,50]. A patch of GTN 10 mg is applied to the skin and if contractions have not diminished after one hour, a second GTN patch may be applied. Therapy with daily patches is continued. Transdermal GTN has minimal effects on maternal pulse, blood pressure and fetal heart rate[51].

Magnesium sulphate (MgSO4) given as 4 gm bolus dose followed by an iv infusion of 1gm/hour is a safe drug, and is currently used as a tocolytic agent in America[52]. However, women receiving MgSO4 should be closely monitored during treatment. The additional neuroprotection of the pre term neonates when antenatal MgSO4 therapy is given to women at risk of PTD is now well established[53]. Approximately 45% of all cases of cerebral palsy are associated with preterm birth. The rate of cerebral palsy amongst neonatal survivors born at less than 28 weeks gestation is up to 30 times higher compared with infants born at term[54]. MgSO4 might be neuroprotective due to its effects on cellular metabolism, cell death or injury or blood flow to the brain. The first case control study was published fifteen years ago and the evidence has been growing ever since[55]. A meta analysis of five trials with 6145 infants has shown that antenatal MgSO4 given to women at risk of PTD substantially reduces the risk of cerebral palsy in their newborn (Relative Risk 0.68, 95% Confidence Interval 0.54 to 0.87)[56].

Antibiotic therapy

Although the role of inflammation in the pathophysiology of spontaneous PTL is well documented there is no evidence that the routine use of antibiotics in the management of PTL reduces PTD[57] A meta-analysis of the 11 trials including 7428 women showed a reduction in maternal infection with the use of prophylactic antibiotics (relative risk 0.74, 95% confidence interval 0.64 to 0.87) but failed to demonstrate a benefit or harm for any of the prespecified neonatal outcomes viz. respiratory distress syndrome and necrotizing enterocolitis[58]. Furthermore women with spontaneous PTL with intact membranes and no evidence of overt infection should not be routinely prescribed antibiotics because there is a possible increased risk of functional impairment and cerebral palsy in their babies[59].

Erythromycin has been recommended for 10 days following the diagnosis of PPROM[60,61]. The use of antibiotics following PPROM is associated with a significant reduction in chorioamnionitis, the numbers of babies born between 48 hours and 7 days, neonatal infections and the number of babies with an abnormal cerebral ultrasound scan prior to discharge from hospital[62].

If group B streptococcus (GBS) is isolated in a woman with PPROM, antibiotics should be given in line with the recommendation for routine intrapartum prophylaxis. Benzylpenicillin 3 g intravenous should be given as soon as possible after the onset of labour and 1.5 g 4-hourly until delivery. Clindamycin 900 mg should be given intravenously 8-hourly to those allergic to benzylpenicillin[63].

The American College of Obstetricians and Gynaecologists recommends a 48 hour course of intravenous ampicillin 2 g dose every 6 hours and intravenous erythromycin 250 mg dose every 6 hours followed by 5 days of oral amoxicillin 250 mg dose every 8 hours and enteric coated erythromycin (erythromycin base 333 mg dose) every 8 hours during expectant management of PPROM, to prolong pregnancy and to reduce infections and gestational-age-dependent neonatal morbidity. The use of the combination of ampicillin-clavulinic acid is not recommended because of its association with an increased rate of neonatal necrotizing enterocolitis[60-62,64].

Conclusions

PTD still remains the leading cause for neonatal morbidity and mortality. Prediction and prevention of PTD remains a challenge for obstetricians as most of the PTDs occur in women with low risk. Ultrasound assessment of cervical length and vaginal progesterone treatment have revolutionized prediction and prevention of PTL. The role of cervical cerclarge has decreased. The diagnosis of PTL remains mainly clinical and the investigations would assist in the management. In PTL of <34 weeks gestation, tocolytics should be considered to delay the delivery by approx 48 hours and allow the administration of corticosteroids or to arrange an *in utero* transfer. Currently nifedepine and atosiban are recommended for this purpose. However, MgSO4 is gaining prominence as a tocolytic in PTL especially because of its neuroprotective effects on preterm neonates. The narrow therapeutic margins of MgSO4 needs close monitoring for possible toxicity. Administration of antibiotics is indicated only in PPROM and in GBS positive women. With the recent advances in the understanding of the aetiology and mechanism of PTL, and the development of newer techniques in prediction, prevention and management of PTL, a universal consensus guideline on this subject should be developed. ■

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