CURRENT CONCEPTS IN MANAGEMENT OF PRETERM LABOUR-A REVIEW ARTICLE

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Abstract

Prematurity remains a leading cause of neonatal morbidity and mortality in developed countries. It causes 60–80% of infant deaths without congenital anomalies. 1-2% of all deliveries are below 32 weeks’ gestation, whereas, it causes 50% of all long term neurological morbidity & 60% of perinatal mortality. Diarrhoea, malnutrition, lower respiratory tract infection have declined but prematurity remains leading cause of morbidity in South East Asian countries. India has worst performance only above Afghanistan in terms of preterm birth and its morbidities, according to Global burden of disease report, 2013. Paradigm of premature deliveries in India is changing; now it is a disease of marginalized as well as affluent. Hence, this review article emphasizes on current management concepts i.e. role of tocolysis, corticosteroids, and other management issues pertaining to prevention and management of preterm labour.

Keywords: Preterm labour, Progesterone therapy, Tocolytics

Introduction

Onset of labour before 37+0 weeks is defined as preterm labour. It is the single most important factor responsible for the increased rates of neonatal morbidity and mortality in both developing as well as developed nations worldwide.1 Preterm births account for 10-15% of all live births worldwide. Preterm labour may be either spontaneous in onset (45-50%) or iatrogenic in nature (15-20%). They may (30-40%) or may not be associated with premature rupture of membranes.2

It is now well recognised that babies born prematurely are associated with both short term and long term complications. Short term complications include conditions like respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and retinopathy of prematurity. Long term complications include neurodevelopment disorders like cerebral palsy, vision and hearing loss, chronic lung disease and gastrointestinal problems.

Proper management of preterm labour and birth is essential in determining the future outcome of the child. The concepts in the management of preterm labour have been changing over the decades and will continue to do so in the future, as newer advances and trials take place in this field of obstetrics.

Antenatal corticosteroids: lung maturation

The lack of foetal lung maturation is a major cause of morbidity and mortality in preterm infants. The use of antenatal corticosteroids to accelerate foetal lung maturity and prevent the resultant respiratory distress syndrome is well documented (ACOG Level A).3 A Cochrane review of 21 trials conducted in 2006 concluded that a single course of corticosteroids when given to mothers at risk of preterm delivery prevents respiratory distress syndrome (Relative Risk 0.66, 95% CI 0.59 to 0.73).3 There is also a significant reduction in the neonatal mortality (RR 0.69, 95% confidence interval (CI) 0.58 to 0.81), cerebroventricular haemorrhage, necrotising enterocolitis, intensive care admission and systemic infections in the first 48 hours of life.

Other agents like phenobarbital and Vitamin K have been tested for use in prevention of intra and periventricular haemorrhage but have not found to have any significant impact.4,7

Which is better? The Dexamethasone v/s Betamethasone debate

Several studies have been done to ascertain the best corticosteroid and the most suitable regimen of the single course of corticosteroid available to prevent the complications associated with preterm births. Most studies have compared betamethasone with dexamethasone. A Cochrane trial of 12 studies concluded that although dexamethasone has a higher rate of prevention of intraventricular haemorrhage in preterm infants (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.21 to 0.92) there is no overall significant difference between the two groups of steroids in regard to other outcomes affecting foetal morbidity and mortality.4

When to give?

All women who are at risk of preterm birth between 24+0 and 34+6 weeks of gestation should be given antenatal steroids (ACOG &RCOG level A).4,9 In women between 23+0 and 23+6 weeks at high risk of preterm delivery may be offered steroid administration (RCOG level C).9

Special cases:

- Elective LSCS: When elective LSCS is planned before 38+6 weeks antenatal corticosteroids should be administered (level A).

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Multifoetal pregnancy: Same dosing and schedule as singleton pregnancy is recommended (level C).

Diabetes Mellitus: There is no contraindication to give antenatal steroids in women with impaired glucose tolerance or diabetes (level D).

Intra uterine growth restriction: Antenatal steroids are recommended between 24+0 and 35+6 weeks of gestation in women with foetal growth restriction (level C).

**Dosing**

ACOG & RCOG (level A) have recommended two doses of betamethasone, 12 mg given intramuscularly 24 hours apart or four doses of dexamethasone, 6 mg given intramuscularly 12 hours apart. There appears to be no benefit of shorter dosing intervals.\(^4\)\(^,\)\(^9\)

**Repeat course: is it justified?**

A repeat course of steroids in mothers who are still at risk of preterm birth before 34 weeks, even 7 days after the first course, has shown no significant benefit or harm to the neonate in early childhood. Short term advantages in terms of fewer incidences of respiratory distress and serious morbidity in first few weeks of life have been documented.\(^10\) ACOG recommends a single repeat course of corticosteroids (level B). RCOG recommends a repeat course only when the first dose has been given before 26 weeks of gestation (level A).\(^4\)\(^,\)\(^9\)

**Magnesium Sulphate: Neuroprotection**

The risk of cerebral palsy in preterm neonates has now become well documented. In a Cochrane review in 2009 which include 5 trials involving 6145 babies concluded that prenatal magnesium sulphate therapy when given to mothers at risk of preterm births has proved to be a very good neuroprotective agent reducing the incidence of cerebral palsy considerably (relative risk (RR) 0.68; 95% Confidence interval (CI) 0.54 to 0.87).\(^11\)

**When to give?**

ACOG recommends the use of magnesium sulphate for neuroprotection in infants where birth is anticipated before 32 weeks of gestation (level A).\(^4\)

RCOG recommends the use of magnesium sulphate for neuroprotection in women with high risk of preterm birth before 30 weeks of gestation where the magnitude of effect is likely to be largest.\(^12\)

**Dosing**

A Cochrane review done in 2012 for comparison of different magnesium sulphate regimens didn’t come to any conclusion as to which one is the best, as no trials comparing the different regimens have been completed yet.\(^13\)

Various regimens by different authors have been suggested. Almost all have used a loading dose of 4-6gm of magnesium sulphate slow intravenous. But the use of maintenance infusion has been variable. Some did not use any maintenance infusion and those who did use in varied doses ranging from 1gm/hr, 2gm/hr or 2-3gm/hr. Although no guidelines are available but RCOG scientific impact paper in 2011 recommended the University of Adelaide guideline which suggested an intravenous 4 g loading dose over 20–30 minutes followed by a 1 g/hr maintenance regime to continue for 24 hours or until birth whichever is earliest. But if birth is not anticipated 12 hours after administration it may be discontinued.\(^14\)

However the doses used for neuroprotection are less than that for tocolysis and hence additional tocolysis (indomethacin has been used with few side effects) may be required.

**Role of tocolysis**

A large number of tocolytics have been used in the prevention of preterm labour with variable results. There is no conclusive evidence that tocolysis improve the foetal outcome but their use helps in prolongation of pregnancy, provide time for the action of steroids and magnesium sulphate for foetal lung maturation and neuroprotection respectively (ACOG & RCOG level A).\(^4\)\(^,\)\(^15\) They also help in providing sufficient time for intrauterine transfer of mother to a centre with better NICU facility. ACOG recommends that women with preterm contractions without cervical changes generally shouldn’t be treated by tocolytics as only 10% of such patients actually deliver. Tocolytics should not be used in conditions where continuation of pregnancy itself is contraindicated (RCOG level B).\(^15\)

**Contraindications to Tocolysis**\(^4\)

- Intrauterine foetal demise
- Lethal foetal anomaly
- Non reassuring foetal status
- Severe eclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis
- Preterm premature rupture of membranes (in the absence of maternal infection)
- Maternal contraindications to tocolysis (agent specific)

**Betamimetics**

The role of betamimetics has been the most widely researched in the prevention of preterm labour. A Cochrane review published in 2014 reported the results of 12 trials involving 1367 women. The results showed that betamimetics reduced the number of women with preterm labour giving birth within 48 hours (average risk ratio (RR) 0.68, 95% confidence interval
The role of magnesium sulphate in the prevention of preterm labour is controversial. Although magnesium sulphate acts as a neuroprotective agent and prevents cerebral palsy in the preterm infant but at the doses required to produce tocolysis they have serious maternal and foetal effects. The Cochrane review in 2002 involving over 2000 women in 23 trials suggested that the risk of neonatal death was higher when exposed to magnesium sulphate (RR 2.82, 95% CI 1.20-6.62). Both ACOG & RCOG don’t recommend use of magnesium sulphate as a tocolytic.

**Oxytocin receptor antagonists**

Oxytocin receptor antagonists have been extensively studied and have proved to have good tocolytic properties. Atosiban is a nonapeptide oxytocin analog which is a competitive antagonist of oxytocin induced contractions. The Cochrane database review conducted in 2014 included 14 trials involving 2485 women. Although there was no significant difference in terms birth less than 48 hours after trial entry when compared to both betamimetics (RR 0.89, 95% CI 0.66 to 1.22) and calcium channel blockers (average RR 1.09, 95% CI 0.44 to 2.73). However, ORA resulted in less adverse maternal effects when compared to betamimetics (RR 0.05, 95% CI 0.02 to 0.11) and CCBs (RR 0.38, 95% CI 0.21 to 0.68).

ACOG in 2012 suggested that Atosiban appears to be the only tocolytic that has shown superiority as maintenance therapy over placebo in prolonging pregnancy. RCOG has concluded that Atosiban along with Nifedipine have comparable effects in prolonging pregnancy upto 7 days and are associated with less maternal adverse effects as compared to betamimetics (level A).

**Cyclo-oxygenase inhibitors**

A number of trials involving COX inhibitors have concluded that these drugs are well tolerated in women when compared to other tocolytics and fewer women needed to stop treatment because of the adverse effects (RR 0.07; 95% CI 0.02-0.29)(RCOG level 1 evidence). A Cochrane review of 13 trials in 2005 showed that when compared to a placebo the use of these agents resulted in reduced number of births before 37 weeks of gestation (relative risk (RR) 0.21) and increase in the birth weight (Weighted mean difference 716.34 gm.). Most of these studies used Indomethacin as the agent.

ACOG has recommended the use of COX inhibitors as 1st line tocolysis (level A).

**Other tocolytic agents**

A number of other agents like nitric oxide donors (Glyceryl trinitrate) and relaxin have been studied. Although they have shown effective tocolysis but the data supporting them is

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insufficient and varied. Further trials would be needed to assess the maternal and foetal effects of these agents.

The use of combination of tocolytics in order to improve the side effect profile and improve neonatal outcomes has been associated with higher incidence of adverse effects and hence not recommended (both ACOG & RCOG level B).\textsuperscript{4,16}

**Maintenance therapy**

After an episode of threatened of threatened preterm labour pains a decision has to be taken on the need for continuation of tocolytic therapy to prevent any future similar episodes. Current data from the various Cochrane trials suggest that further tocolytic therapy after arrested preterm labour does not improve the maternal or neonatal outcome significantly (ACOG level A).\textsuperscript{4} However, the trials available provide insufficient data to draw any conclusions from and require further studies with larger number of cases to establish the real role of maintenance therapy.

**Therapeutic agents in preterm labour**\textsuperscript{24}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Maternal Side Effects</th>
<th>Foetal Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Adrenergic Receptor Agonists:</strong> Ritodrine, Terbutaline</td>
<td>Ritodrine: 0.05-0.15mg/Min Maximum Upto 0.30 mg/Min Terbutaline: 0.25 mg S/C Every 20mins To 3hrs.</td>
<td>Tachycardia, Hypotension, Tremors, Palpitationspulmonary Edema, Hypokalemia, Hyperglycemia</td>
<td>Foetal tachycardia</td>
<td>Poorly Controlled Maternal Diabetes &amp; Tachycardia Sensitive Maternal Cardiac Disease</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers:</strong> Nifedepine</td>
<td>Loading Dose 20 mg followed By 10-20 mg 3- 4 Times A Day</td>
<td>Dizziness, Flushing, Hypotension, Bradycardia and Elevation of Liver Enzymes</td>
<td>No known adverse effects</td>
<td>Hypotension, Aortic insufficiency</td>
</tr>
<tr>
<td><strong>Magnesium Sulphate</strong></td>
<td>Loading: 4-6gm Iv Over 20 Mins followed By 2-3gm/Hr Infusion</td>
<td>Flushing, Nausea, Respiratory and Cardiac Depression, Loss of Tendon Reflexes</td>
<td>Neonatal depression</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td><strong>Oxytocin Receptor Antagonists:</strong> Atosiban</td>
<td>Loading Bolus Dose 6.75mg followed By Infusion At 18mg/Hr For 3 Hrs And 6mg/Hr Upto 45 Hrs.</td>
<td>Chest Pain, Palpitations, Headache, Dyspnea, Injection site reactions</td>
<td>No known adverse effects</td>
<td>Autoimmune conditions</td>
</tr>
<tr>
<td><strong>Cox Inhibitors:</strong> Indomethacin</td>
<td>Loading Dose Of 50-100mg Followed By 25 mg 4-6 Hrly</td>
<td>Nausea, Gastritis, Esophageal Reflux, Platelet dysfunction</td>
<td>Patent Ductus Arteriosus, Oligohydramnios, Necrotizing Enterocolitis</td>
<td>Platelet dysfunction, Hepatic dysfunction, Hepatic dysfunction and Asthma</td>
</tr>
</tbody>
</table>
Progesterone therapy

Accumulating evidence suggests that the myometrial activity associated with preterm labour results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role in this regard. Recent data suggest that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium. It is now clear that, although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labour, the onset of labour both at term and preterm is associated with a functional withdrawal of progesterone activity at the level of the uterus. It is data such as these that provide the rationale behind the use of progesterone supplementation to prevent preterm labour and birth.

The role of prostagstational agents (either alone or in combination with other tocolytics) has been studied in various trials. Cochrane review of 8 trials involving 563 women in 2014 suggested that use of progesterone therapy reduces the frequency of uterine contractions, prolongs pregnancy and arrests cervical shortening. As the data available was relatively small no conclusions were drawn.

ACOG in 2012 recommended that a woman with a singleton pregnancy with prior history of spontaneous preterm birth should be given progestational support in the form of vaginal progesterone starting at 16-24 weeks of gestation irrespective of the cervical length (level A). In women who are not at a high risk of preterm birth but incidental USG findings revealed a short cervix (< 20mm) should also be given oral or vaginal progesterone therapy. However its use in multiple gestation is not recommended (level A).

At present RCOG doesn’t recommend the use of progesterone in women at high risk of preterm delivery and its use should be limited to clinical trials to determine whether its use is associated with improved fetal, neonatal, and/or infant outcome.

The optimal progesterone formulation, route of delivery, and dose for the prevention of preterm birth has not yet been determined. These agents include progesterone powders, capsules, and gels as well as injectable progesterone in-oil. They can be given vaginally, orally, or by injection. Recent formulations of sustained release preparations 300 or 400 mg can deliver a high concentration of progesterone with least side effects of oral preparations. Oral administration of natural micronized progesterone as sustained release (SR) preparation offers consistent tissue concentrations for endometrial support offering once a day dosage convenience thereby improving the patient compliance. The slow, sustained release kinetics of progesterone by SR formulation minimizes drug exposure to liver metabolic enzymes at individual time points, thereby offering sustained action with minimal central side effects including drowsiness due to the active metabolite Allopregnanolone. In a recent prescription event monitoring study by Purandare AC et al, to assess the safety profile of oral natural micronized progesterone sustained release in india, it was concluded that Oral NMP SR is a clinically feasible option for LPS especially in bad obstetric history (BOH) cases having insignificant side effect profile for improved compliance.

Cervical cerclage

Cervical cerclage in women with singleton pregnancy at high risk of preterm labour and a cervical length less than 25mm before 24 weeks of gestation has shown to result in a reduction of 30% in the risk of preterm delivery before 35 weeks. Hence ACOG (Level A) and RCOG (Level B) recommend the use of prophylactic cerclage in these women.

Role of pessary

Use of cervical pessary has been proposed as a minimally invasive procedure as compared to cervical cerclage in women with incompetent cervix. A Cochrane review done in 2013 on the role of cervical pessary included only one trial of 385 women with short cervix. The randomised clinical trial concluded that the use of the cervical pessary significantly reduced the rates of preterm births (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.27 to 0.49). Also there was a statistically significant reduction in the need for tocolytics (RR 0.63; 95% CI 0.50 to 0.81) and corticosteroid therapy (RR 0.66; 95% CI 0.54 to 0.81). But more trials would be needed to conclusively prove the beneficial role of cervical pessary in women with short cervix.

Role of rest and hydration

Rest and hydration have been proposed to increase the uterine blood flow and subsequently decrease the uterine contractility. A Cochrane research done in 2004 however, found that there was no decrease in the incidence of preterm birth when bed rest was compared to no intervention at all (7.9% in the intervention group versus 8.5% in the control group). A similar Cochrane review in 2013 involving 228 women compared the effects of intravenous hydration with bed rest. The authors did not find any difference between the two groups in terms of risk of preterm delivery or admission to NICU rates. Both the reviews concluded that there is no substantial effect of rest and hydration in the management of preterm labour and shouldn’t be routinely recommended.
Role of intramniotic surfactant

Theoretically, use of intramniotic surfactant therapy in women at risk of preterm birth would reduce the need for neonatal endotracheal intubation and the resultant complications of bronchopulmonary dysplasia and chronic lung disease. A Cochrane review done in 2010 to assess the role of intramniotic surfactant did not find any trial which matched their selection criteria. More randomised trials are therefore required to come to any conclusion regarding this therapy.

Prophylactic antibiotics

The use of prophylactic antibiotics in women with preterm labour with intact membranes with no evidence of overt infection is controversial. Presence of intrauterine infection leads to a series of inflammatory reactions which increases the risk of brain injury in preterm infants leading to cerebral palsy. The Overview of the Role of Antibiotics in the Curtailment of Labour and Early Delivery (ORACLE II) trial showed a non-significant increase in functional impairment (RR 1.10, 95% CI 0.99 to 1.23) and cerebral palsy (CP) (RR 1.82, 95% CI 0.99 to 3.34) when use of any antibiotic was compared to use of no antibiotic in pregnancy. This may be due to the fact that the foetus may continue to be exposed to an inflammatory environment despite resolution of infection. Hence, both ACOG and RCOG don’t recommend prophylactic antibiotic in this group of patients (level A). This despite the fact that these women may be at a high risk for group B streptococcus infection.

However when there was evidence of maternal infection prophylactic antibiotics significantly reduced maternal and infant morbidity and mortality.

Role of bacterial vaginosis

Bacterial vaginosis has been known to be associated with preterm births, premature rupture of membranes and chorioamnionitis. But till date no evidence has been found to show that screening and treatment of bacterial vaginosis improves the neonatal outcome and prevents preterm births. Hence both ACOG &RCOG doesn’t recommend routine screening and use of antibiotics for treatment of bacterial vaginosis.

Role of probiotics

Probiotics are live microbes such as lactobacillus which provide some amount of immunity to the host. They are available as both oral as well as vaginal preparations. It has been theorised that these friendly bacteria fight against vaginal infections and modulate the immune response thereby influencing the inflammatory response which is responsible for preterm labour. However, a Cochrane review in 2007 which included a total of three trials done to assess the role of probiotics in preterm labour showed that although there was a 81% reduction in genital infection in these women (RR 0.19; 95% CI 0.08 to 0.48) but that did not translate into prevention of preterm births or reduction in the neonatal morbidity or mortality. The authors concluded that currently there was insufficient data to analyse the role of probiotics in preterm labour.

Labour & Delivery

The issues related to labour and delivery of preterm infants has been widely studied but currently no recommendations are available regarding this aspect.

Caesarean section versus vaginal delivery

Although a caesarean delivery appears to be protective for the preterm infant but traumatic injuries to mother are not uncommon. In the Cochrane review of 2013 no significant difference was found between the two groups in terms of neonatal birth asphyxia (RR 1.63, 95% CI 0.84 to 3.14), perinatal deaths (RR 0.29, 95% CI 0.07 to 1.14) and abnormal follow up in childhood (RR 0.65, 95% CI 0.19 to 2.22).

Early versus delayed cord clamping

The effect of early versus delayed cord clamping has been extensively studied in cases of preterm infants. Data from Cochrane review of 2012 suggest that delayed cord clamping (till the flow of blood through the umbilical vein stops) decreases the incidence of intraventricular haemorrhage (RR 0.59, 95% CI 0.41 to 0.85), necrotizing enterocolitis (RR 0.62, 95% CI 0.43 to 0.90) and lesser need for blood transfusion for anaemia (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.46 to 0.81).

Conclusion

Previous preterm birth is highest risk factor for preterm delivery. The obstetricians should avoid unnecessary preterm inductions. Obstetricians need to be sensitized for prevention of preterm births due to associated hazards. Once a patient lands into preterm labour, not much can be done for management. Best approach lies in prevention of preterm labour. Universal cervical length screening may be considered for prevention of preterm birth.

References


