Chapter

Preterm Labour

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Abstract

Preterm delivery is defined as delivery before 37 weeks completed gestation. It represents a major cause of neonatal morbidity and mortality and accounts for 5–10% of all deliveries. Cervical length assessment between 16–24 weeks and positive fetal fibronectin beyond 21 weeks gestation are proved to useful tools in prediction of preterm labour. Treating asymptomatic bacteruia and bacterial vaginosis in high-risk women reduces the incidence of preterm labour. Cervical cerclage is recommended to reduce the incidence of preterm birth in women with 2nd trimester losses and those with cervical length of 25 mm or less on transvaginal ultrasound between 16–24 weks gestation. Atosiban and nifidipine are currently the agents of choice in tocolysis. Antenal steriods in womens with threating preterm labour reduces the perinatal morbidties. Magnisum sulphate role is established for neuroprotection especially in extreme gestations between 24–30 weeks. Vaginal delivery is mode of choice for delivery with consideration to avoid fetal blood sampling, fetal scalp electrodes and ventouse prior to 34 weeks gestations. Caesarean section is considered for obstetric reasons that guide labour management at term.

Keywords: definition, maternal morbidity, feral morbidity, risk factors, tocolysis, antenatal steroids

1. Introduction

Preterm delivery is defined as delivery before 37 weeks completed gestation. It represents a major cause of neonatal morbidity and mortality in both developed and developing countries with European and North American figures ranges between 5–10% of all deliveries. In the UK it represents 7.3% of live births

Extreme preterm birth is defined as preterm birth prior to 28 weeks gestation. It accounts for 5–10% of preterm deliveries. The major concern of extreme preterm birth is the significant risk of neonatal mortality as the survival rates are very low at these gestations (0.4% at 22 weeks, 7% at 24 weeks) while the main concern of preterm births above 28 weeks is the neonatal morbidity as the survival rates are 77% at 28 weeks and 97% at 36 weeks.

2. Aetiology

The aetiology of preterm labour is multifactorial with a common pathway reslut-ing in increased relasee of prostaglandins and cytokines within the cervix, myome-trium and fetal membranes. The release of prostaglandins is triggered by infective or inflammatory process [1], uterine overdistension as in cases with polyhydraminons and mutiple preganacy or choriodecudidual haemorrhage as in cases with abruption.

In modern obstetrics, 30–40% of preterm deliveries are iatrogenic. The most common cause of which is severe pre-eclampsia associated with intrauterine growth restriction (IUGR) and antenatal fetal distress. Other common iatrogenic preterm deliveries include, Grade 3 and 4 placenta praevia or placenta abruption with major bleeding, sever IUGR with absent or reversed end-diastolic flow. It is also notable that the increased number of large loop excision of transformation zone (LLETZ) procedures for abnormal cervical cells leads to cervical scarring and iatrogenic cervical incompetence and hence preterm delivery.

3. Prediction of preterm labour

Identifying high risk patients is crucial in managing and preventing preterm labour. Prediction of preterm labour is possble through; risk assessment, uterine activity monitoring, cervical length assessment and fetal fibronectin assessment.

3.1 History taking and risk assessment

Patients with previous preterm labour are at higher risk of having pretem term birth. The risk is 17% after one previous preterm delivery and increases to 28% after two preterm deliveries. Patients with previous preterm premature rupture of membranes (PROM) [2], previous second trimester loss and thoese who are known to have cervical incomptence and congenital uterine anaomalies are at higher risk for preterm birth. Fruther more uterine overdistention as with Polyhydraminos and mutiple pregnancy is associated with preterm delivery. Patient with placental abruption are also known to be at higher risk of preterm labour.

Scoring systems were developed in attempts to achieve accurate and numerical score to help the management of preterm labour. However; the scoring systems proved to have poor sensitivity and poor postive predictive values as more that 50% of preterm labour occurs in the first pregnancy and in womens with no risk factors [3]**.**

3.2 Monitoring uterine activity

It notable that uterine activity increases prior to onset of pretrm labour by 24 hours. However, the use of home uterine contraction monitors or self palpations has not proven to be useful as they had poor postive predictive vlaues and their use did not improve the perinatal outcomes.

3.3 Assessment of cervical length

Clinical assessment of cervical status in terms of dilatation, softening and effacement can predict preterm labour, However it has low sensitivity and repeated vaginal examination in it self may incease the cervical prostaglandins relase and subsquently increase the incidnce of preterm labour.

Utrasound assessment of cervical length is a reliable method and highest predictive value up to 70% is notable with cervical length under 25 mm in womens with risk factors for preterm labour. Serial cervical length assessment is recommended in hight isk group between 16–24 weeks. Cervical length is best measured by transvaginal scan with empty bladder as full bladder may lead to false increase in the cervical length measurments. The risk of preterm labour increases from 1% at cervical length of 25 mm to 4% at 15 mm cervical length. The marked increased risk is notable at 5 mm cervical length with preterm birth risk of 78% [4, 5].

Cervical length assessment is not routine in womens with no risk factors for preterm birth as the positive predictive value is low in this group. Also, preventive interventions as cervical cerclage is not recommended in low risk group as they have shown no improvement in the outcome in this group [4].

The presence of funnelling of the internal os is another helpful finding in predicting the preterm birth, However, it is less accurate compared to cervical length assessment due to inter and intra observer variations [6].

3.4 Fetal fibronectin testing

Fetal fibronectin is normally present in high concentration prior to 21 weeks of gestation in cervical and vaginal secretions prior to membranes fusion. Inflammatory process, uterine overdistension and choriodecidual haemorrhage increase fetal fibronectin secretion after 21 weeks gestation.

Fetal fibronectin testing by swabbing the posterior fornix or ectocervix between 22 and 34 weeks gestation in recommended as postive results in high risk group especially in presence of symptoms warrant admistration of steriods and hospital admission. Fetal fibronectin testing is not recommeded in womens with no risk factors as it has not shown to be effective in improving the outcome despite more than half of preterm birth occurs in this group [7].

Testing for fetal fibronectin is contraindicated before 22 weeks gestation, in presence of preterm premature rupture of membranes, active vaginal bleeding and intercourse in the previous 24 hours.

Other biochemical markers such as Insulin like growth factor binding protein-1, interleukin-6, interleukin-8 and tumour necrosis factor-alpha (TNF-α) were assessed in research setting for use in predicting preterm labour. However, none of those markers is currently used in routine practice [8].

4. Neonatal morbidity and mortality of preterm labour

Preterm birth is associated with significant neonatal morbidities such as respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity, neonatal sepsis, intraventricular haemorrhage and periventricular leucomalacia. Longterm impact of prematurity are mainly cognitive and motor impairement which are more prevelant in extreme preterm births. Prolongation of pregnancy with tocolytic agents and adminstration of antenatal steriods signficantly reduces the neonatal morbidities in preterm births [1, 9].

EPICure data [9] may be useful tool in counselling the parents about fetal prognosis. Neonatal mortality is higher with preterm birth at lower gestational ages with survival rate of 7% at 24 weeks compared to 77% at 28 weeks and 97% at 32 weeks. The survival rates improves 2.2% daily between 24 and 28 weeks gestions. Preterm delivery at 36 weeks is associated with 99% survival rate [1, 9, 10].

5. Prevention of preterm delivery

Mutiple preventive measures were tested for prevention of preterm labour such as treatment of asymptomatic bacteruria and bacterial vaginosis, prophylactic antibiotics in womens with postive fetal fibronectin and reduced cervical length, cervical cerclage, prophlactic tocolysis and hormonal supplements. Some were proved to be effective in reducing preterm deliveries while others shown no significant diffierence in the outcome regarding the incidance of preterm birth and its associated morbidities.

a. Bacterial vaginosis occurs in 10–22% of pregnant womens with unknown aetiology. Treating the bacterial vagnoisis and hence reducing its associated inflammatory process was proved to reduce the incidance of preterm birth in womens with risk factors for preterm labour especially those with postive fetal fibronectin testing. Asymptomatic bacteruria occurs in 2–9% pregnant womens and its associated inflammtory process can participate in increasing prostagladins levels in cervicovaginal secretions and hence the preterm birth. Treating asymptomatic bacteruria in high risk group reduces the incidence of preterm birth but not in low risk group.

b. Antibiotic treatment for prophylactic antibiotics in womens with postive fetal fibronectin and in womens reduced cervical length in absence of infective or inflammatory process is not recommeded due to limited evidence and lack of proven efficacy.

c. Cervical cerclage proved to reduce the incidence of preterm birth in women with 2nd trimester losses and those with cervical length of 25 mm or less on transvaginal ultrasound between 16–24 weks gestation [4, 11]. Cervical cerclage can be done by transvaginal route (McDonald or Shirodkar techniques) or transadominal route when there is insufficient cervical tissue to hold the suture or when the vaginal approach has failed previously [1, 4]. Counselling prior such procedure is essential to involve the pros and cons. Complications of the procedure can include; bleeding, infection (endometritis), increased frequency of contractions, cervical trauma, preterm premature rupture of membranes, suture displacement, sepsis, cervical scarring. Cervical cerclage is contraindicated in presence of fetal anomaly, intrauterine infection, active bleeding and preterm premature rupture of membranes [1, 6].

d. Prophylactic tocolysis for high risk women has not proved to reduce the preterm birth rate and is not recommended.

e. Progesterone supplement via vaginal or intramuscular route on weekly basis till 36 weeks can be considered to promote reduction of uterine activity. Its use is limited to clinical trials in European guidlines [12, 13] while the recent NICE guideline in UK and in North America, progesterone supplementation is recommended for clinical use for reuction of preterm births [1, 14].

f. Use of cervical pessaries, bed rest and restrticting physical activity and intercourse have no proved evidence of preventing preterm labour [15, 16].

6. Management of preterm labour

The mangement of preterm labour fall into five areas; the use of tocolysis, adminstration of antibiotics, admistration of antenatal steriods, magnisum sulphate for neuroprotection and finally the considerations for the mode of delivery.

7. Tocolysis

It is important to realise that the aim of tocolysis in modern obstertics is limited to gain few days to allow admistration of antenatal steriods which proved to reduce perinatal morbidities in preterm birth and allow in utero transfer (**Table 1**).

Tocolytics	Mechanism	Dose	Side effects	Contraindications
Ritodrine - b2-agonists Currently not in use	b2-receptor stimulation reduces free intra-cellular Ca^{+2} via cyclic AMP and hence muscle relaxation	50–100 μ g/min IV then, increase by 50 μ g/min every 10 min. (up to 350 μ g/min)	Maternal; Hyperglycemia hypokalemia Tremors and nervousness Dyspnea and chest pain Palpitations and arrhythmia Hypotension Pulmonary edema Fetal/neonatal; Tachycardia Hypoglycemia Hypocalcemia Hyperbilirubinemia hypotension IVH	Dysrhythmias or other significant cardiac disease Diabetes mellitus Uncontrolled thyroid disease
Calcium channel blockers (CCB) - Nifedipine Currently first line	Inhibit influx of calcium into cell and hence prevent myometrial contraction	20–30 mg, then 10–20 mg every 4–8 hours (max 90 mg/day)	Maternal; Transient hypotension, headache and dizziness, Nausea Flushing Fetal/neonatal; None	Cardiac disease Hypotension Use with magnesium (collapse) Use with caution in renal disease
Atosiban - Oxytocin receptor antagonists Currently second line	Competitively inhibit oxytocin receptors	6.75 mg IV bolus, then 300 μg/min every 3 hours. (max 45 hours)	Maternal; Minimal; Nausea and vomiting Hot flushes Hypotension and dizzness Fetal; None	None
Cyclo-oxygenase (COX) inhibitors Non-selective; indomethacin Selective (COX-2 inhibitor); sulindac nimesulide	Inhibition of COX leads to reduced PGs synthesis and hence myometrial relaxation	Indomethacin: 50–100 mg loading dose, then 25–50 mg every 6 hours for max 48 hours Sulindac: 200 mg every 12 hours for max 48 hours.	Maternal; Minimal if used for 48 hours; Less with COX2 inhibitors; Peptic ulcerations Thrombocytopenia Postpartum haemorrhage Allergic reaction. Fetal; Main concern; premature closure of ductus arteriosus Risk of neonatal necrotizing enterocolitis, IVH and renal dysfunction	Renal or hepatic disease Active peptic ulcer Uncontrolled hypertension NSAID-sensitive asthma and thrombocytopenia
Magnesium sulfate (MgSO4) Currently not in use	Intracellular calcium antagonist	Initial: 4–6 g/30 min, then: 2–4 g/h	Maternal; Headache and flushing Lethargy Muscle weakness and diplopia Dry mouth Pulmonary edema Fetal/neonatal; Lethargy Hypotonia Hypocalcemia Respiratory depression	Myasthenia gravis

Table 1.
Tocolytics.

8. B2-agonists

Ritodrine and other b-agonists as terbutaline, salbutamol were used as tocolytic agent but currently not recommeded as first line due to its maternal and neonatal side effects. They act on b2 receptors in myometrial smooth muscles via a cAMP dependent mechanism leading to reduction in the intracellular calcium causing muscular relaxation. Cochrane review on B2-agonists concluded that they decrease the number of preterm births within 48 hours but not within 7 days [1, 17, 18].

Maternal side effects include; palpitations and arrhythmias, chest pain, hypotension, flushing, nausea, headache, pulmonary oedema, hypokalaemia and hyperglycaemia. Neonatal side effects include; tachycardia, hypotension, hypoglycaemia, hypocalcemia and ileus. It is not proved that B2-agnosists are associated with neonatal periventericular haemorrhage [18].

9. Indomethacin

It is a nonsteroidal anti-inflamatory agent which inhibit cyclo-oxygenase enzyme and subsequently reduces myomeytrial prostaglandins concentration which inturn down regulates myometrial cells gap junctions, down regulates oxytocin receptors and reduces intracellular calcium levels. It has better tocolytic effect and better safety profile than b-agonists but its routine use is limited due to the associated fetal side effects [18].

Maternal side effects include; risks of peptic ulcerations, thrombocytopenia and postpartum haemorrhage and allergic reaction. Fetal side effects include; premature closure of ductus arteriosus. There is risk of neonatal necrotizing enterocolitis, intraventericular haemorrhage and renal dysfunction [18].

10. COX (cyclo-oxygenase)-2 inhibitors

It is a nonsteriodal anti-inflammatory agent which act specifically on cycloxgenase-2 enzyme which is upregulated in preterm labour. The mechanism of action is simillar to indomethacin but with better maternal side effect profile. Its routine use is limited due to fetal concerns over premature closure of the ductus and renal idysfunction [18].

11. Atosiban

Atosiban is an oxytocin analogue competitively blocks oxytocin and vasopressin receptors leading to reduced intracelluar calcium and lesser prostagladins production. It is recommended and licenced in preterm labour [1, 18, 19]. Its side effects include; maternal nausea, vomiting, hot flushes, hypotension and dizzness. It has simillar effectivness to B2-agonists and nifidipine but with a safer profile however, it is more expensive and given intravenously [1, 18].

12. Nifedipine

It is a calcium channel blocker that is proved to be effective in reducing preterm birth with lesser side effects compared to B2-agonists. It is admnistered orally and it is considered first line treatment option [1, 18]. The side effects of its use include; headache, dizzness, ankle odema, and constipation.

13. Magnesium sulphate

Cochrane review did not support its use for tocolysis as studies repeorted did not show that magnesium sulphate delayed or prevented preterm birth [18].

14. Antibiotics

The use of antibiotics is recommeded with preterm premature rupture of membranes (PPROM) based on ORACLE trial and chochrane review which proved that they reduce the time to delivery and the incidence of chorioamnionitis. They also decrease the ioccurance of neonatal sepsis and the need for neonatal surfactant and oxygen therapy. On the other hand; the ORACLE trial did not recommed its use in preterm labour without premature rupture of membranes as there was no difference in the neonatal outcomes [1, 20, 21].

It is also concluded that erythromycin is a better choice compared to coamoxiclav in women with preterm labour associated with premature rupture of membranes due to increased risk of necrotizing enetrocoilitis with the use of co-amoxiclav [20, 21].

15. Antenatal steriods

The Royal College of Obstetricians and Gynaecologists (RCOG) recommeded the use of antenatal corticosteriods in women with threating preterm labour as it is proven that their use has significant reduction in neonatal respiratory distress syndrome, intraventricular haemorrhage and neonatal death without increase in neonatal sepsis in women who has preterm labour and PPROM.

The use of antenatal steriods is recommeded with threatening preterm labour between 24 weeks and 34 weeks gestations may be considered up to 35 + 6 weeks with the optimal benefit within a window of one to seven days [1, 22].

The agent of choice is betamethasone as it has lesser risk of periventericular leucomalacia compared to the use of dexamethasone [22].

It is recommeded that betamethasone is adminstered intramuscularly in patients with preterm labour as the oral adminstration is associated with higher risk of neonatal sepsis and intraventricular haemorrhage. It is recommended to be used as two doses of 12 mg, 24 hours apart.

The use of mutiple courses of antenatal steriods is not recommeded as per RCOG guidance as it is associated with increassed risks of maternal osteoprosis, infection and imparied glucose tolerance. Multiple courses of steriods is associated with fetal risks including; intrauterine growth restriction, low birth weight, necrotizing enterocolitis, adrenal insufficiency and abnormal neurological development. Compared to a single course, mutiple courses have no benefit of improving neonatal respiratory distress syndrome, chronic lung disease and intraventericular haemorrhage [1, 22].

16. Magnisum sulphate for neuroprotection

Children born to women given magnesium sulphate for seizure prevention in severe pre-eclampsia were noted to have lower rates of cerebral palsy. This is possibly because magnisum decreases extracellular glutamate with hypoxia and hence reduces excitotoxicity. It also limits calcium influx through voltage-gated channels and in turn reduces the activation of apoptosis. Further more it reduces oxidative stress and reduces the production of pro-inflammatory cytokines.

It is use for neuroprotection is recommeded for use in women with established preterm labour or planned to hace elective preterm birth within 24 hours at gestations between 24 and 30 weeks. It is can be considered between 30 and 34 weeks [1, 23].

17. Mode of delivery

Vaginal delivery is considered to be appropriate choice in gestations under 24 weeks as the neonatal survival rate is very low. The challanging decision is the balance of vaginal delivery versus caesarean section in preterm delivery between 24 weeks and 37 weeks gestation [1, 24].

The decision for caesarean section is recommended to be for the obstetric reasons such as malpresentations and intrapartum fetal distress. Cochrane review for elective caesarean section in women with threating preterm labour between 24 and 37 weeks gestation has not shown statistically significant difference in the neonatal outcomes with regard the incidence of respiratory distress syndrome and neonatal seizures.

There is no evidence to support routine prophylactic outlet forceps or episiotomy when considering vaginal delivery between 24 and 37 weeks gestations. It is advisable to leave the fetal membranes intact till late in labour to reduce the risk of cord prolapse. The fetal scalp electrode and fetal blood sampling use is contraindicated prior to 34 weeks gestation and hence any suspicious fetal monitoring trace should be considered as indication for caesarean section. Their use is considered between 34 and 36 weeks gestation. It is also important to note that ventouse delivery is contraindicated prior to 34 weeks gestation. Consideration should be taken for caesarean section in preterm delivery with breech presentation [1, 24].

Delayed cord clamping for at least 30 seconds but no longer than three minutes is advisable in preterm deliveries to allow auto transfusion of the baby. Senior obstetrician should be consulted in planning the delivery and the decision-making throughout the labour [1, 24].

Parents should have discussion with joint obstetric and neonatal team prior embarking onto labour is helpful to ensure their understanding of challenges for the preterm baby such as ability to maintain stable core body temperature, ability to breath spontaneously and feeding difficulties. The expected postnatal care for the preterm baby should be planned as detailed as possible with the parents and ensure the availability of the facilities.

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