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# Challenges of pre-maturity: the obstetrician's role

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### Introduction

WHO definition of a premature delivery is a baby born before 37 completed weeks of gestation. It is the leading cause of death worldwide for children below 5 years of age. About 10% of all live births globally are pre-term<sup>1</sup>. Asian and sub-Saharan countries account for 80% of preterm births globally. Preterm births appears to be increasing in most countries<sup>2</sup>. Preterm newborns are classified into four groups. Late-preterm 34 - 37 weeks (incidence 70%), moderate preterm 32 - 34 weeks (incidence 13%), very preterm 28 - 31 weeks (incidence 10%), and extremely preterm - less than 28 weeks (incidence 7%). Preterm children are prone to both short and long term illnesses. Short-term problems include respiratory distress syndrome, intraventricular haemorrhage, sepsis, jaundice, necrotizing enterocolitis and feeding problems. Long-term complications include learning disabilities, speech and language disorders, visual disturbances, neurological and behavioral disorders and cerebral palsy. The relative risk of a preterm infant developing cerebral palsy is nearly 40 times that for a term infant. Approximately 10% of surviving newborns weighting less than 1 kg at birth will develop cerebral palsy. The three main causes of premature birth are spontaneous (45%), maternal or fetal infection (30%) and pre-term premature rupture of the membranes (PPROM). Proper obstetric management of the pre-term labour (PTL) can significantly affect the prognosis for the pre-mature neonate.

## Prediction of preterm labour

The two most important tests to predict PTL are the trans cervical measurement of cervical length and fetal fibronectin test.

Using trans vaginal ultrasonography, if the cervical length is more than 15 mm it is unlikely that she is in preterm labour. If the cervical length is 15mm or less the woman is in pre-term labour<sup>3</sup>.

Fetal fibronectin is the most powerful biochemical marker identified to predict premature labour. Fetal fibronectin is a glycoprotein found in the extracellular matrix and when found in the vagina or cervix it is a marker of chorio-decidual disruption. Fetal fibronectin is absent from the vagina from around 20 weeks until term. The most important characteristic of fetal fibronectin is its negative prediction value. In a woman suspected of preterm labour if the test is negative (concentration 50mg/ml or less) the chances of delivery in the next week or two is less than 1%. If the test is positive the risk of delivery with in the next two weeks is about 20%.

### **Prevention of preterm labour**

Management options available for prevention of premature labour consist of vaginal progesterone and cervical cerclage high-risk patients. Theories in that existwith regard to initiation of labour include progesterone withdrawal, oxytocin initiation and pre-mature decidual activation.

A meta analysis of six randomized control trials of 17 - hydroxyl progesterone caproate used prophylactically to prevent preterm labour revealed a significant decrease in preterm birth (odds ratio 0.5, confidence interval 0.3, 0.85). 95% However the use of progestins including large doses of intramuscular progesterone, 6-methyl-17 acetoxyprogesterone has not successfully inhibited active pre-term Current recommendation is to labour. with vaginal commence treatment progesterone between 16 - 24 weeks and to continue until 34 weeks in high-risk women<sup>4</sup>.

Cervical cerclage should be considered in following situations:

- Past spontaneous pre-term birth (up to 34 weeks)
- Past cervical tears, cone biopsy, LLETZ
- PPROM in a previous pregnancy
- When transvaginal ultrasound done between 16 – 24 weeks show a cervical length of 25mm or less

Rescue cervical cerclage should be considered for women between 16 - 27weeks of pregnancy with a dilated cervix and exposed unruptured membranes. This is performed as an emergency procedure. Cervical cerclage is not offered to women with signs of infection, active vaginal bleeding and in the presence of active uterine contractions.

# Symptoms of preterm labour (PTL)

Women in PTL usually present with intermittent abdominal pain. If speculum and digital examination confirms the possibility of pre-mature labour the woman is suspected to be in premature labour. The woman is considered to be in established PTL if she has progressive cervical dilatation from 4cms with regular contractions. If the clinical history, initial assessment, speculum examination and swab for fetal fibronectin suggests that the woman is in suspected PTL treatment for PTL should be initiated. The therapeutic interventions considered in the management of PTL generally have two goals. Either to inhibit or reduce the strength of uterine contractions and delay the time of delivery or to optimize the fetal condition before preterm delivery.

## Measures to delay the labour

Measures to inhibit or reduce the strength of uterine contractions include tocolytic therapy. Tocolytics stop contractions temporally but rarely prevent preterm birth. Although delivery may be delayed long enough for administration of corticosteroids, treatment does not result in improved peri-natal outcome. Tocolytics can delay the birth until in-utero transfer to appropriate neonatal health care settings. There is no benefit of maintenance of tocolytic therapy. The decision as to which tocolytic agent should be used as first line therapy for an individual woman should be based on multiple factors including efficacy, gestational age, presence of maternal co-morbidities, and the frequency and severity of side effects<sup>5</sup>.

Calcium channel blockers (nifedapine):

Myometrial activity is directly related to cytoplasmic free calcium and a reduction in its concentration inhibits contractions. Nifedapine reduce the risk of delivery within 48 hours in women suspected of preterm labour (PTL) between 24 - 34 membranes<sup>6</sup>. weeks with intact nifedapine Combination of with magnesium is potentially dangerous since nifedapine enhances neuromuscular blocking effects of magnesium interfering with pulmonary and cardiac functions. If nifedapine is contraindicated oxytocin receptor agonists can be considered (atosiban).

Nitric acid donors administered orally, trans dermally or intravenously was not effective in preventing PTL. Maternal hypotension is a common side effect.

**Betamimetics** are currently not recommended in prevention of PTL because the side effects are very frequent and serious. Cox inhibitors and Calcium channel blockers may be the best tocolytics in terms of pregnancy prolongation, improvement of neonatal outcome and risk of maternal side effects. Calcium channel blockers does not carry the risks of oligohydramnios and premature closure of ductus arteriosus observed with cox inhibitors (indomethacin)<sup>6,7</sup>. The use of maintenance therapy with a tocolytic agent following an initial treatment of threatened preterm labour is not recommended. The use of a combination of tocolytic agents for delaying preterm birth is also not recommended.

### Vaginal microbiome and PTL

Microbiome is the pattern of microorganisms present in a defined environment. Lactobacillus sp. are the predominant vaginal commensal in pregnancy. There is good evidence of an association between reduced lactobacillus sp. and the risk of PTL<sup>8</sup>. Lactobacillus sp. dominance have a protective effect against PTL. Infections that have been associated with PTL are bacterial vaginosis, aerobic vaginitis, trichomoniasis, gonorrhoea and chlamydia<sup>9</sup>. Colonisation of the vagina with pathogenic bacteria activates the innate immune system of the vagina, cervix and decidua causing an inflammatory cascade. Many studies have reported an association increased vaginal between microbial diversity and risk of  $PTL^{10}$ . Therefore antibiotics have the potential to prevent spontaneous PTL. A recent Cochrane meta-analysis summarising 8 randomised control clinical trials comparing antibiotic therapy (mostly penicillin derivatives) with

a placebo for the treatment of PTL demonstrated no difference between the placebo and antibiotic treated in pregnancy prolongation, pre-term delivery, respiratory distress syndrome or neonatal sepsis<sup>11</sup>.

Use intra-partum of antibiotics are recommended when intrapartum infections diagnosed. Tests to diagnose are intrapartum infections are C-reactive proteins, white cell count and CTG - fetal tachycardia. It is not recommended to use any one of the above in isolation to confirm or exclude intra-uterine infection. If the tests are not consistent with each other continue to observe the woman and repeat tests.

# Premature preterm rupture of membranes (PPROM)

A woman is considered having PPROM if she has ruptured membranes before 37 weeks of pregnancy but is not in established labour. PPROM is associated with 25 - 30 % of pre-term deliveries. When PPROM occurs there is a significant increase in the risks of neonatal morbidity and mortality. Spontaneous sealing of the membranes occur in less than 10% of cases. Diagnosis of PPROM is by speculum examination and observing pooling of amniotic fluid. If amniotic fluid is not observed perform insulin like growth factor binding protein-1 test or placental alphamicroglobulin- 1 test on vaginal fluid. If the above tests are negative and no amniotic fluid is observed do not offer prophylactic antibiotics. antenatal Nitrazine test to diagnose PPROM is not recommended due to its low sensitivity. Antibiotics play a critical role in the management of women with PPROM. Aim of antibiotics is to avoid maternal and fetal infection and to prolong the pregnancy. A recent Cochrane review of 12 trials involving 1680 infants found that use of antibiotics when compared to no antibiotics in PPROM resulted in a 33% reduction of

neonatal infections. A Cochrane review also evaluated maternal outcomes among 11 trials and there were lower rates of chorio-amnionitis in the group with antibiotics<sup>12</sup>. Based on this meta-analysis there is a clear benefit to the mother and the neonate with the use of anti-biotics in PPROM.

In 1997 Mercer and colleagues showed in a landmark controlled clinical trial that the of ampicillin and erythromycin use improved the neo-natal outcome in  $PPROM^{13}$ . Since then most studies comparing alternative regimes have been published. Several studies have shown that the use of co-amoxiclav increases the risk of necrotising enterocolitis by 4 times<sup>14</sup>. Meta-analysis have been done among the studies using 3 day versus 7 day courses. The current recommendation from American College of Obstetricians and Gynecologists (ACOG) is for a 7-day course of antibiotics. For women with no penicillin allergy ampicillin 2g intravenously 6 hourly for 48 hours and continue with amoxicillin 250mg 8 hourly for another 5 days with erythromycin 250mg intravenously every 6 hourly for 48 hours and to continue 333mg 8 hourly for another 5 days is recommended. For women with penicillin allergy clindamycin 900mg intravenously 8 hourly and gentamicin 5mg/kg intravenously daily for 48 hours and to continue with clindamycin 300mg 8 hourly for 5 days. ACOG currently does not recommend the use of antibiotics when PPROM is managed expectantly after 34 weeks. For Group B streptococci (GSB) positive women with PPROM after 34 weeks GBS prophylaxis The recommended should be given. antibiotic is penicillin (5 million units intravenously and then 2.5 million units every 4 hours or if unavailable ampicillin 2g intravenously and then 1g every 4 hours) is recommended. In the presence of allergy to penicillin, the treatment should be based on sensitivity to erythromycin and clindamycin. Until sensitivity results

become available vancomycin should be used for prophylaxis.

### Measures to optimise fetal condition

Measures to optimise the fetal condition before delivery includes maternal corticosteroids and intravenous magnesium sulphate.

Maternal corticosteroids are indicated in women between 23-36 weeks with suspected or established PTL, having planned PTL, or PPROM. Corticosteroids results in a significant decrease in the incidence of respiratory distress syndrome and a decrease in perinatal mortality by  $31\%^{15}$ . The beneficial effect was noted only if delivery occurred after more than 24 hours had elapsed from the first dose and before 7 days from the last dose. In a recent meta-analysis of 32 randomised controlled trials involving more than 3300 women with PPROM it was shown that antenatal corticosteroids reduced the risk of respiratory distress syndrome and intraventricular haemorrhage significantly. There was no increase in maternal or neonatal infection rates<sup>15,16</sup>. 12mg of betamethasone on two occasions 24 hours apart or 6 mg dexamethasone 12 hourly for 4 doses are the currently recommended regimes. When offering repeatcourses of cortico-steroids consider the interval since the end of last course, gestational age and the likelihood of birth within the next 48 hours. In PPROM it is recommended to administer only a single rescue dose as multiple doses can lead to an increased risk early onset neonatal of sepsis, chorioamnionitis, and endometritis<sup>17</sup>.

Several randomised control studies have evaluated the efficacy of MgSO<sub>4</sub> for prevention of cerebral palsy. Meta-analysis of findings concluded that MgSO<sub>4</sub> significantly reduces the risk of cerebral palsy<sup>18</sup>. Therefore it is recommended to offer MgSO<sub>4</sub> for neuroprotection for women between 24 – 34 weeks when in established pre-term labour or planned to undergo pre-term birth within 24 hours. 4g of MgSO<sub>4</sub> is given intravenously over 15 minutes and continued at the rate of 1g per hour for 24 hours or till birth. Maternal monitoring of a woman on MgSO4 should include recording the pulse, blood pressure, respiratory rate and the deep tendon reflexes every 4 hourly and to monitor the urine output hourly. If the woman develops signs of oliguria monitoring should be more frequent and consider reducing the dose of MgSO<sub>4</sub>. Neonatal effects of MgSO<sub>4</sub> are neuroprotective from 23-32 weeks, reduced incidence of cerebral palsy at 3 years and minimization of the effects of infection.

### Fetal monitoring in PTL

Fetal monitoring of a woman in premature labour should include CTG monitoring. A normal trace is reassuring but an abnormal trace does not necessarily indicate fetal hypoxia. Also there is no evidence to show that CTG improves the outcome of preterm labour when compared with intermittent auscultation<sup>4</sup>. Use of fetal scalp electrode for fetal heart rate monitoring in women in established labour before 34 weeks is not recommended unless it is not possible to monitor with external CTG or the benefits are likely to outweigh the potential risks.

### Mode of delivery

Caesarean delivery is recommended in women in labour between 26-37 weeks pregnancy with a breech presentation<sup>19</sup>. In women with a cephalic presentation there are no known benefits or harm for the baby from caesarean section<sup>20</sup>. Consider the risks of caesarean section in PTL such as a poorly formed lower segment which will result in a vertical uterine incision and its implications for future pregnancies. At threshold of viability, caesarean delivery is not offered unless the fetal weight is estimated at 750g or greater at 24 weeks. When deciding the mode of delivery consider the fetal presentation, indication for preterm birth such as severe intrauterine growth retardation, pre-eclamptic toxaemia, initial intended route of delivery and fetal status. Current data does not show any deference in neonatal mortality in neonates delivered vaginally or abdominally. Operative vaginal delivery is relatively contraindicated in preterm foetuses less than 34 weeks. Use of vacuum is associated with a raised risk of intracranial haemorrhage, extracranial haemorrhage and brachial plexus injury when compared with other modes of delivery $^{21}$ .

### Delayed clamping of umbilical cord

It is estimated that 25-60% of the total blood volume of the feto-placental circulation is stored in the placenta. Three quarters of the transfusion of blood from the placenta to the fetus occurs in the first minute after birth<sup>22</sup>. Delayed clamping of the cord leads to an expansion in intravascular volume that facilitates the cardio-pulmonary transition. Meta-analysis of randomised control trials have shown that with delayed clamping of the cord there is a significant reduction in need for blood transfusion. intracranial haemorrhage, necrotising enterocolitis and neonatal mortality in fetuses less than 32 weeks. Before clamping the cord position the baby below the level of the placenta and wait at least 60 seconds but no longer than 3 minutes before clamping the  $cord^{23}$ . If the baby needs to be moved away from the mother for resuscitation consider milking the cord 3 times over a duration of less than 30 seconds.Uterotonic agents following birth and before cord clamping increase the rate of placental transfusion and enhance the effect of delayed clamping $^{24}$ .

### Conclusions

The obstetric practices discussed have the potential to substantially decrease neonatal morbidity and mortality in preterm neonates. The evidence in support of most practises is quite strong. Each institution should prepare specific protocols of care and conduct and should carryout periodic audits to verify their consistent implementation.

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