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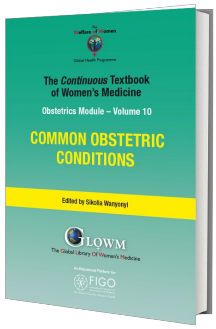

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Chapter

Preterm Labor: Suspected and Confirmed

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INTRODUCTION

Preterm labor (PTL) is defined as uterine contractions leading to effacement and dilation of the cervix before 37 completed weeks of gestation. It ***may*** result into preterm birth (PTB) which is delivery occurring less than 37 weeks of gestation.[1] Preterm birth affects approximately 10–18% of all pregnancies worldwide and leads to early infant morbidity, mortality and chronic childhood diseases. The rate of preterm birth in the developed and developing countries is increasing and it accounts for over one million deaths in children below five years of age. The situation is worse especially in developing countries where access to neonatal and infant care services are limited.[2,3] Preterm labor and birth are of multifactorial origin ranging from fetomaternal conditions, infections, lifestyle and stress.[4] Preterm labor is classified based on gestational age; mild preterm (32–36 weeks), very preterm (28–31 weeks) and extremely preterm (<28 weeks). There is a challenge in accurately estimating gestational age in many resource limited settings. The objective of this chapter is to help to improve the readers understanding of the mechanism of preterm labor, clinical diagnosis and management based on latest evidence for practice.

Epidemiology

About 15 million preterm births occur each year with 7% of these infants dying from preterm birth related complications. Indeed, 75% of the total infant mortality is related to preterm birth with a vast majority (85%) of global preterm births occurring in Asia and Africa, where health care resources to take care of the babies born too soon are limited.[5,6] Preterm birth causes a range of long term complications in surviving children including but not limited to; sepsis, necrotizing enterocolitis, respiratory distress syndrome, intraventricular hemorrhage, hypothermia, hyperbilirubinemia,

hypoglycemia, retinopathy of prematurity, neurodevelopmental impairment and cerebral palsy. There are associated economic burden related to long term neonatal intensive care services, care of the resultant long term complications and lost time from work.[7,8]

Risk factors for preterm labor and birth

Preterm labor is a syndrome with multiple risk factors and causes. The following have been implicated to increase a woman's risk of preterm labor:[9,10,11]

1. Infections such as chorioamnionitis, Human Immunodeficiency virus, malaria, Group B streptococcus, Bacterial vaginosis
2. Previous history of preterm birth or late miscarriages
3. Low socioeconomic status
4. Smoking and alcohol intake
5. Poor nutrition or malnutrition
6. Multiple gestation, short intergestational interval and extremes of maternal age, either too young or too old
7. Placental abnormalities such as antepartum hemorrhage or abruption;
8. Uterine abnormalities such as over-distention due to polyhramnios and cervical incompetence
9. Other maternal complications such as preeclampsia, diabetes, stress, hormonal changes, and fetal abnormality or disorders

Depending on the antecedent cause, preterm labor and birth are classified into two broad categories:

1. spontaneous preterm birth that is characterized by spontaneous onset of labor or prelabor premature rupture of membranes (pPROM)) accounting for 70% of preterm births and
2. medically indicated preterm birth advertently initiated by a medical practitioner before 37 completed weeks for maternal or fetal indications.

Mechanisms of preterm labor and birth

The actual pathophysiology underlying preterm labor is hitherto unknown. There are some similarities between term labor and preterm labor such as uterine contractility, cervical dilatation and effacement representing. These similarities represent the final common pathways of the two processes. During a normal pregnancy, progesterone is responsible for maintaining the uterine quiescence by ***suppressing genes responsible for production of***; proinflammatory cytokines and chemokines (a shift from the inflammatory state), contraction associated proteins (such as oxytocin, connexin 43), prostaglandins receptors, and matrix metalloproteinases. This suppression is achieved via the zinc finger E-box binding homeobox proteins ZEB1 and ZEB2 at their promoter site.[12,13,14]

During labor, there is apparent increase in expression of micro-RNAs (miRNAs) specifically the miR-200 family which promote catabolism of progesterone and down regulation of ZEB1 and ZEB 2. Consequently, there is an increase in expression of the contraction-associated genes with formation of oxytocin receptor and connexin-43, and enhancement of oxytocin-induced contractility in the myometrial cells. The increase in matrix metalloproteinases induces cervical ripening and dilatation via weakening of collagen cross-linkages, dissolution of fibronectin, and an increase in glycosaminoglycans, a component of extracellular matrix. The aforementioned pathway leads to decidual activation resulting into membrane separation and rupture.[14,15,16]

It has been suggested that infectious agents and their products attach to toll-like receptors (TLRs) resulting in change in gene expression in cells that eventually lead to progesterone withdrawal and biochemical changes described above to cause PTL. In contrast, the preceding mechanisms for non-infectious preterm labor is not well understood but could be via the hypothalamus-pituitary-ovarian axis.

CLINICAL APPROACH

History

A patient with suspected of PTL will usually present with a history of low back pain, uterine contractions that are increasing in frequency and duration, pressure in the pelvis/perineum, and vaginal spotting. Some may present with pPROM with passage of liquor. Assessment of age, ethnicity or race, weight and nutritional status and gestational age, based on last normal menstrual period (LNMP) and first trimester ultrasound examination should be inquired. A history assessing risk factors for preterm birth has to be noted. This include history taken under the following segments:

1. The history of the presenting illness:
   Whether intensity and frequency of contractions have been increasing, drainage of liquor, color, quantification, and duration, perception of fetal movement, aggravating factors if known such as stress, anxiety, depression, life events, any fever, any history of abdominal trauma or lifting of heavy objects.
2. In the past medical history:
   Take note of any history of any abdominal surgery, active use of medication, allergies and known medical conditions.
3. In the obstetrics and gynecological history:
   Note the parity, index prenatal care and history of previous pregnancies such as multiple gestations, polyhramnios, pPROM, second trimester abortion, cervical cerclage/surgery, urinary tract infections, placenta previa, placental abruption, previous preterm delivery and the gestation, history of fetal anomalies including intrauterine growth restriction, any other medical complication in the current pregnancy. In the gynecology history consider any known uterine or cervical anomaly, sexually transmitted infections, and contraception.
4. In the family and social history:
   Note the patients' lifestyle including smoking, use of alcohol and substance abuse, socioeconomic status, educational level, occupation, Maternal first-degree family history of spontaneous preterm birth. A history of patient being a preterm places her in a high-risk category. Of the predictors of preterm birth, past obstetric history may be one of the strongest predictors of recurrent preterm birth.[17]

Clinical examination

Check for the following in patients that present with preterm labor; general status of the patient, any signs of anemia, weight, vital signs, temperature may be normal or raised, pulse rate (may be raised in case of an infection), respiratory rate, blood pressure. Assessment of contraction frequency, duration, and intensity. Examination of the uterus to assess fetal heart rate, firmness, tenderness, fetal size, and fetal position. A speculum examination to look for pooling of amniotic fluid in the posterior fornix. If pooling is not noted take a sample of vaginal fluid for performing an insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test. Check for cervical dilatation and effacement. Digital vaginal examination is not encouraged, but may be done to assess cervical dilatation and effacement after the possibility of placenta previa and rupture of membranes have been excluded. The general cervical and uterine examination findings have to be in keeping with findings of a normal term labor for it to qualify as preterm labor.

Investigations

The aim of investigations is to confirm the diagnosis of PTL and provide direction for further management. They are divided into laboratory investigations, imaging and fetal monitoring.

Laboratory investigations:

1. Cervical smear for fetal fibronectin (fFN) test, fFN is a uniquely glycosylated form of the abundant plasma protein fibronectin, found at the uteroplacental junction and the amniotic fluid. It is released into the upper vagina near the onset of labor. It has a high negative predictive value for preterm birth. Its absence in the upper vaginal tract sample rules out labor within 7 days with a very high negative predictive value (97–99.5%). A positive test is equivocal and should not be used to make a diagnosis of PTL.
2. Cervical smear for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP1). This factor is secreted by decidual cells and leaks into cervical secretions when fetal membranes start separating from decidua. Just like fFN, phIGFBP1 has a high negative predictive value (92% specificity) of preterm birth but poor sensitivity.
3. Cervical smear for microbiology, about 30% of all preterm labor and births are related to infection and inflammation generated by infection. The samples are tested for Bacterial vaginosis, GBS, Chlamydia and other infective associated with PTL and PTB.

4. Vaginal pH for diagnosis of infection, a high vaginal pH is an indicator of Bacterial vaginosis
5. Tests for Interleukins, proteases and antioxidants in the cervical samples have also been used to confirm the process of PTL.
6. Full blood count and C-reactive protein to assess any shift in white and red blood cell counts. C-reactive protein as a marker of inflammation.

Imaging studies:

1. Abdominal ultrasound to verify the status of the fetus, amniotic fluid volume, fetal development and multiple gestation and to also rule out the differentials.
2. Transvaginal ultrasound- a shorter cervix less 25 mm is associated with a relatively higher risk of preterm delivery. The predictive value of a negative test is high (92%); this implies that pregnant women who are found not to have a shortened cervix can be reassured, and unnecessary therapeutic measures can be avoided

Fetal monitoring

1. Cardiotocography (CTG)
   CTG is excellent in confirmation of uterine contractions and frequency. Its use in fetal monitoring remains controversial. A Cochrane review found no evidence to support the use of antepartum CTG for improving perinatal outcomes in preterm fetuses[18] although most of the included studies were underpowered to make an indisputable conclusion. Interpretation of fetal heart rate in preterms is subject to effect of multiple developmental milestones and stages of maturation of various fetal systems. In the presence of a non-reassuring CTG trace, it is recommended that fetal scalp blood sampling is done to detect acidosis and confirm actual fetal distress. Fetal scalp sampling is contraindicated in pregnancies complicated with HIV, Hepatitis B or C.

Diagnosis and differentials

Diagnosis of preterm labor is made when a patient presents with symptoms of regular painful uterine contractions increasing in frequency and intensity accompanied by cervical dilation and/or effacement before completion of 37 weeks of gestation. There are a number of other clinical conditions that may mimic PTL.

1. Urinary tract infection – this may present with abdominal pain that may mostly be non-intermittent, dysuria, previous history of UTI and increased urinary frequency and urgency. UTI may lead to PT through the infection/inflammation pathway.
2. Ovarian cyst/torsion – this is a rare diagnosis in pregnancy, it will normally present with nonspecific signs of abdominal pain or backache. May present with tachycardia, low BP, nausea and vomiting, or localized abdominal pain.
3. Appendicitis – Abdominal pain may be higher in the abdomen and more diffuse. May have accompanying symptoms of nausea, vomiting, and loss of appetite.
4. Placental abruption – In concealed abruption, signs of fetal distress may be present without per vaginal bleeding. Otherwise there is vaginal bleeding with increased likelihood of preterm labor.

Management/treatment

The main aim of intervention is to increase the chances of a best outcome for both the fetus and the mother. Thus, based on presenting and prevailing clinical circumstances, the management protocol may dictate whether immediate delivery or prolongation of pregnancy to allow room for more intervention is essential. Interventions aimed at prolonging the pregnancy should be reserved only for those in which obvious delay will be of benefit to the neonate. For pregnancies that are below 34 weeks of gestation, prolongation of these pregnancies by at least 2 days to allow for administration of glucocorticoids for fetal lung maturation and maybe referral to a centre with a better perinatal care including neonatal care units may be relevant. Its worthwhile to note that about 30% of preterm labor resolve spontaneously and out of all the patients hospitalized for preterm labor, 50% end up giving birth at term.

Prior to preterm labor

1. a. Cervical cerclage

   In cases where congenital or acquired cervical weakness is known, elective or rescue cerclage may be indicated to prevent preterm delivery or late miscarriages. Transvaginal techniques either McDonald or Shirodkar may be used. It is thought that cerclage also reduces the risk of ascending intrauterine infection in addition to supporting the cervix.

   b. Progesterone

   Progesterone administration has been shown to reduce the risk of preterm birth and neonatal morbidity in women at high risk of PTL. Either vaginal progesterone or intramuscular 17α-hydroxyprogesterone caproate have been used for the prevention of preterm birth. Available data suggests that administration of progesterone in the second trimester to women with short cervix or with a previous history of PTL may reduce their risk for preterm birth.

   c. Bed rest

   There is no evidence that bed rest actually lowers the rate of preterm birth although it is plausible to suggest that restricting physical exertion may help women at high risk of premature labor by limiting stress on the gravid uterus. There may no benefit to women already in in preterm labor.

2. For treatment purposes

   a. Tocolysis

   Tocolytic therapy may provide short-term prolongation of pregnancy to buy time for the administration of antenatal glucocorticosteroids and magnesium sulfate for neuroprotection, as well as referral. There is no evidence to suggest direct neonatal outcome benefit besides prolongation of pregnancy. This treatment is to be given for as short a time as possible and promptly terminated once contractions have ceased and should not be continued for more than 48 hours except in cases such as placenta previa and amniotic sac prolapse. Various agents have been used as tocolytics agents:

   i. Calcium channel blockers are the most preferred because of less side effect profile. They inhibit both the direct influx of calcium into myocytes and the release of intracellular calcium thereby maintaining uterine quiscence. Nifedipine is the the most commonly used calcium antagonist. It is given as an initial dosage of 20 mg orally, followed by 20 mg orally after 30 minutes. If contractions persist, therapy can be continued with 20 mg orally every 3–8 hours for 48–72 hours with a maximum dose of 160 mg/d. After 72 hours, if maintenance is still required, long-acting nifedipine 30–60 mg daily can be used. Other advantages of nifedipine include reduction in neonatal intraventricular hemorrhage, respiratory distress syndrome, and necrotizing enterocolitis. Its side effects, including nausea, flushing, headache, palpitations, and reflex tachycardia.

   ii. Magnesium sulfate is given as an initial loading dose of 4–6 g IV over 20 minutes, followed by a maintenance dose of 1–4 g/h depending on urine output and persistence of uterine contractions. Maternal baseline investigations have to be within normal range. Common maternal side effects include flushing, nausea, headache, drowsiness, and blurred vision. The mother should be monitored for toxic effects, such as respiratory depression or even cardiac arrest. Magnesium sulfate has been found to have neonatal neuroprotection advantage besides its use as a tocolytic.

   iii. Oxytocin antagonists (atosiban) bind competitively to the oxytocin receptor inhibiting the oxytocin-mediated rise of the intracellular calcium concentration. They have a less side effect profile compared to the other agents. Maternal side effects are mild headache, nausea and vomiting.

   iv. Indomethacin has been used as a tocolytics agent in PTL pregnancies of about 30 weeks or less complicated with polyhydramnios. Indomethacin acts on both fetal renal system to reduce polyhydramnios and decidual macrophages to reduce prostaglandin synthesis. It is given as an initial dose of 100 mg per rectal followed by oral dose of 50 mg every 6 hours for 8 doses. Precaution against oligohydramnios should be taken by monitoring amniotic fluid index.

   v. Betamimetics inhibit myometrial contractions by raising the intracellular concentration of cAMP. Fenoterol, ritodrine, terbutaline, and salbutamol are used. For salbutamol, start with a dose of 10 microgram/min IV increase according to response until contractions diminish (max 45 microgram/min) maintain rate for 1 hour after contractions have stopped then reduce by 50% every 6 hours until steroid course is completed. Watch for side effects such as tachycardia, sweating, tremulousness, nausea, or headaches, cardiac arrhythmia and pulmonary edema.

   The following contraindications for Tocolysis should be noted:

   Gestational age greater than 34 weeks

Ascending or contiguous intrauterine infection.

In cases of suspected abruption or obvious antepartum hemorrhage.

Other indications for immediate delivery such as fetal anomaly (not compatible with life), eclampsia, and preeclampsia.

Well considered non reassuring fetal status

b. Glucocorticoid administration

The aim of this treatment is to induce fetal lung maturation. The treatment consists of two 12 mg doses of betamethasone given intramuscularly 24 hours apart, or four 6 mg doses of dexamathasone given intramuscularly 12 hours apart. This treatment has been found to lower neonatal mortality, the risk of neonatal respiratory distress syndrome, the frequency of cerebral intraventricular hemorrhage, and the frequency of necrotizing enterocolitis. There is no data no regarding the efficacy of corticosteroid use before viability.

c. Antibiotics

Although the role of inflammation in the mechanism of spontaneous preterm birth is known, there is no evidence that the routine use of antibiotics in the management of patients with preterm labor has reduced the incidence of preterm birth. Women with pPROM and those that require GBS prophylaxis should receive a 7- to 10-day course of antibiotic therapy that include a macrolide but exclude amoxycillin/clavulanic acid combination.

d. Delivery

Patient should understand the potential outcome of preterm delivery. Attempt to prolongation of pregnancy at an earlier gestation of 20 weeks and before 24 should thoroughly be discussed with the patient and all the information on neonatal morbidity declared. Generally, prolongation of pregnancy with tocolytics in patients with PTL beyond 34 weeks is not indicated. If the fetus is cephalic and there is no other contraindication for vaginal delivery, a vaginal birth should be attempted. Assisted delivery techniques should only be attempted if indicated and with caution to avoid unnecessary complications.

Caesarean section for breech presentation at early gestational age is controversial. A decision for this route of delivery should be discussed between the patient and the attending doctor. A caesarean delivery significantly increases the risk of postpartum hemorrhage and had longer neonatal length of hospital stay compared to vaginal delivery.[19] Specifically, American College of Obstetricians and Gynecologists recommends a delayed cord clamping for at least 30–60 seconds after birth in absence of any contraindication.

A neonatal team must always be at hand for infants requiring immediate resuscitation and to provide care for the newborn.

Follow up

Women who are not delivered immediately should be nursed in the hospital with routine pregnancy monitoring.

After preterm delivery, the affected mothers are at increased risk of morbidity and psychological trauma than their counterparts. They tend to have less enthusiasm for specialist follow-up and this may be a risk in itself. Psychoeducation and counseling significantly reduces the psychological distress and these patients must be identified and treated as soon as possible.

Since women with PTL are at increased risk for future PTL, the attending doctor should discuss with the patient about future fertility and outcomes. They should also put in place measures that are aimed at mitigating some of the modifiable risk factors such as:

1. Preconception care, including encouraging family planning beginning in adolescence and continuing between pregnancies
2. Sexual health programs aimed at prevention and treatment of sexually transmitted infections prior to pregnancy. For those with infections, they should be treated immediately.
3. Behavioral modifications such as stopping stopping to smoke, alcohol use and early antenatal care.

PRACTICE RECOMMENDATIONS

- **Suspected preterm labor occurs when clinical symptoms and examination findings suggest a possibility of preterm labor but rules out established labor. A woman has confirmed preterm labor if she has a positive and has progressive cervical dilatation starting from 4 cm with regular uterine contractions.**
- **Preterm labor (suspected or confirmed) is an entity with many causes and varied outcomes. It calls for a multidisciplinary management effort.**
- **There is evidence to show an increasing burden of preterm labor and birth in many developing countries and North America.**
- **The pathophysiology of preterm labor remains unclear. Infectious causes of PTL may act via the Toll like receptors before the 'final common pathway'. The preceding mechanisms for the non-infectious causes is not known.**
- **Clinical history and examination are important in risk profiling of the patients and in arriving at the diagnosis. Some risk factors put women at a higher risk of preterm labor and birth than others**
- **The aim of investigations is to confirm the diagnosis of PTL and provide direction for further management.**
- **Timely communication amongst the management team pre-delivery and post-delivery ensure acceptable maternal and neonatal outcomes.**
- **Management focusses on prevention and treatment using tocolytics, corticosteroids, antibiotic and referral (as necessary).**

CONFLICTS OF INTEREST

The authors of this chapter declare that they have no interests that conflict with the contents of the chapter.

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