Video Case

Preterm Labor

Objectives:

- → Define preterm labor
- → Identify the modifiable and non-modifiable risk factors and causes for preterm labor.
- → Determine the incidence of preterm labour and its contribution to neonatal morbidity and mortality.
- → Describe the signs and symptoms of preterm labor.
- → Describe diagnostic criteria of preterm labor
- → Describe the initial management of preterm labor.
- → List indications and contraindications of medications used in preterm labor.
- → List the adverse outcomes associated with preterm birth.
- → Describe the counseling for reducing preterm birth risk.

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Female presentation

Video Case | Editing File

Preterm Labor (PTB)

Definition

- Delivery between 20-37 weeks / 24-36 weeks + 6 days of EGA with:
  - ≥3 uterine contractions in 30 min
  - Cervical dilation at least ≥ 2 cm or changing.
- Preterm delivery is the **most common** cause of perinatal **morbidity** (respiratory distress, infection, and intraventricular hemorrhage) **and mortality**.
- Overall, 12% of pregnancies deliver prematurely.
- Many patients will have **preterm contractions** but not be in preterm labor (it is labor if there's BOTH contractions and cervical dilatation).
- Under 20 weeks is always abortion.
- Preterm: 20-36 weeks + 6 days OR 24-36 weeks + 6 days.
- Term: completed 37 weeks - 42 weeks.
- Postterm: After 42 weeks.

Causes & Risk Factors:

- **Prior preterm birth** (PTB). x2 risk
- Cervical abnormalities:
  - Short transvaginal (TV) cervical length (<25 mm) - length assessed by US
  - Incompetent cervix (e.g. Hx of surgery)
- Structural:
  - Premature rupture of membranes (PROM)
  - Placental abnormalities (Abruptio placentae, Placenta previa)
  - Excessive uterine enlargement (Polyhydramnios, Multiple gestation)
  - Uterine anomaly, E.g. Septate, Didelphys, Bicornuate.. Etc
  - Uterine Tumor, E.g. Leiomyoma (Fibroid)
- Maternal:
  - Young patient
  - Low BMI
  - African American race black population is twice as high as that in the white population poor access to, and procurement of antenatal care.
  - Genitourinary Infections.
  - Short inter-pregnancy interval (<18 months).
  - Smoking, substance abuse, vitamin D deficiency.

PATHWAYS THOUGHT TO CAUSE PRETERM BIRTH:

1. Infection (cervical-vaginal-urinary).
2. Placental-vascular.
3. Psychosocial stress and work strain (fatigue).
4. Uterine stretch (multiple gestations).

TABLE 12-1

PRIMARY CAUSES OF PRETERM BIRTH AND THEIR ESTIMATED FREQUENCY

Cause	Frequency (%)
Spontaneous preterm labor	35-37
Multiple gestations*	12-15
Preterm premature rupture of membranes (PPROM)	12-15
Late preterm births	50-70
Pregnancy-associated hypertension	12-14
Cervical incompetence/uterine anomalies	12-14
Antepartum hemorrhage	5-6
Intrauterine growth restriction (IUGR)	4-6

*Increased proportion because of advancing maternal age and assisted reproductive technologies (ARTs). ART has increased the incidence of twinning by 50% with a very recent decline due to more elective single embryo transfers.

Preterm Labor (PTB)

Evaluation:

- Full comprehensive history
- **Provided that membranes are not ruptured and there is no contraindication to a vaginal examination (e.g., placenta previa)**
  - Vaginal examination ⟶ cervical length, dilation, station, presentation.
  - Digital examination (fingers) MUST be avoided
- Labs:
  - **Swap/Culture for presence of Group B strep.**
  - CBC, Random Blood Glucose, Serum electrolytes levels … etc.
  - Ultrasound ⟶ fetal weight, presentation, any congenital malformations, multifetal gestation, uterine anomalies.
- **Examine for chorioamnionitis: fetal / maternal tachycardia + uterine tenderness + fever**
- **Fetal fibronectin (fFN):**
- A protein matrix produced by fetal cells which acts as a biological glue, binding the trophoblast to the maternal decidua. It "leaks" into the vagina if PTB is likely and can be measured with a rapid test using a vaginal swab.
  - Prerequisites for testing: gestation 22–35 weeks, cervical dilation <3 cm, and membranes intact.
  - Interpretation: main value of test is a negative, since chance of PTB in the next 2 weeks is <1%; with a positive result, likelihood of PTB is 50%.
- Any underlying correctable conditions.
- Put patient in lateral decubitus position.
- Monitor uterine activity.

Symptoms:

- Lower abdominal pain/pressure, lower back pain and diarrhea.
- Increased vaginal discharge, or bloody show.
- Particularly in primigravidas symptoms may be present for a number of hours to days but are not recognized as contractions by the patient.

Diagnosis:

Criteria that need to be met to make a diagnosis include:

1. Gestational age: >20 weeks but <37 weeks.
2. Uterine contractions: at least 3 contractions in 30 minutes (4 per 20 min or 8 per 60 min).
3. Cervical exam: serial examinations show a change in dilation or effacement, or a single examination shows cervical dilation >2 cm / cervical effacement of 80%.
   a. Uterine contractions are not a good predictor of preterm labor, but cervical changes are.

Preterm Labor (PTB)

Management of PTB:

1. **Hydration and bed rest** can resolve uterine contractions in 20% of patients.
    - If a patient doesn't respond to hydration and bed rest, start Tocolytic therapy.
2. Confirm labor using the three criteria listed earlier—gestational age, contraction frequency, cervical exam.
3. **Rule out contraindications to tocolysis** (there are contraindications to all tocolytics in general and contraindications to each group alone). Do not try to prolong pregnancy if obstetric, fetal, maternal complications are present.
    - **Obstetric:**
        - **Severe bleeding** (not spotting) **from placenta previa or abruptio placentae.**
        - **Chorioamnionitis**
        - Ruptured membranes**.**
    - Fetal:
        - Lethal anomaly (anencephaly, renal agenesis)
        - Fetal demise or jeopardy (repetitive late decelerations)
        - **IUGR**.
    - Maternal:
        - Eclampsia
        - **Severe preeclampsia**
        - Advanced cervical dilation
4. If no contraindications are present, administer a tocolytic agent if <34 weeks to prolong pregnancy to allow for antenatal steroid effect, also to get time to transfers the patient to other hospital that have NICU (NICU can help within viability limits (24 wks. or greater than 500 g). (tocolytics in detail next slide)
5. **Start IV MgSO4 if <32 weeks for fetal neuroprotection of cerebral palsy.**
    - Administer at least four hours before anticipated birth.
    - MgSO4 can also act as an anticonvulsant (to avoid seizures).
6. **Corticosteroids: administer IM betamethasone / dexamethasone if <34 weeks** to stimulate fetal type II pneumocyte surfactant production. A 48-hr course is needed for full effect to take place.
    - Decreases incidence of respiratory distress syndrome and intraventricular hemorrhage.
7. **Start antibiotic therapy:**
    - **IV penicillin G if <36 weeks for GBS sepsis prophylaxis** (use vancomycin if allergic to penicillin G).
    - For patients who are not allergic to penicillin, a 7-day course of ampicillin and erythromycin may be given. If allergic to penicillin may be given clindamycin.
    - First obtain recto-vaginal cultures.
    - The use of prophylactic antibiotics in women with preterm labor may prevent progression from a subclinical infection to clinical amnionitis.
8. **Delivery in preterm labor is usually vaginally** (normally or outlet forceps), except for very low-birth fetuses (↓1500 g) where cesarean delivery is better, as in 28 wks.

Preterm Labor (PTB)

Tocolytic

- **Parenteral agents may prolong pregnancy, but for no more than 72h. This does provide a window of time for:**
  - Administration of maternal IM betamethasone to enhance fetal pulmonary surfactant.
  - Transportation of mother and fetus in utero to a facility with neonatal intensive care.
  - Oral tocolytic agents are no more effective than placebo.
- MgSO4, Terbutaline, or Nifedipine can be used up to 34 weeks. Indomethacin should not be used after 32 weeks due to concerns regarding in-utero closure of the PDA.
- **441 doctor: You should memorize the contraindications and why it's contraindicated.**

Tocolytic Agents:	Information	Side effects	Contractions
Beta Agonists ex: Terbutaline	Tocolytic effect depends on the β2- adrenergic receptor myometrial activity. Particularly in primigravidas symptoms may be present for a number of hours to days but are not recognized as contractions by the patient.	Tachycardia, **Hypokalemia**, **Hyperglycemia**, Pulmonary edema.	In cardiac disease, diabetes mellitus, uncontrolled hyperthyroidism.
Calcium Channel Blocker ex: Nifedipine	decrease intracellular calcium.	Tachycardia, **Hypotension**, **Myocardial depression.**	hypotension or pre-load dependant cardiac lesions eg. aortic insufficiency.
Indomethacin (NSAID)	It is a Prostaglandin synthetase inhibitors which decrease smooth muscle contractility by decreasing prostaglandin production.	Gastritis, emesis Platelets dysfunction **Oligohydramnios**, **PDA closure in utero with >48 H** **PDA for neonate** Neonatal necrotizing enterocolitis.	in gestational age ≥32 weeks as they may cause premature closure of the ductus arteriosus. Furthermore, they can inhibit uterine contractility. **Bleeding disorder**, **low plt** **GI ulceration and asthma.** **DM**
Magnesium Sulfate (MgSO4)	a competitive inhibitor of calcium. Magnesium overdose is treated with IV calcium gluconate.	Muscle weakness, Respiratory depression & pulmonary edema.	renal insufficiency & myasthenia gravis.

Preterm Labor (PTB)

Complications of PTB:

- Neonatal death
- Respiratory distress syndrome (RDS)
- Patent ductus arteriosus (PDA)
- Intraventricular hemorrhage (IVH)
- Necrotizing enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Bronchopulmonary dysplasia (BPD)
- Cerebral palsy (CP)

Prevention:

- All pregnant women should be screened for history of previous PTB on first prenatal visit and cervical length by sonogram prior to 24 weeks.
- **Interventions to prevent preterm delivery include the following:**
  - **If cervical length >25 mm with prior spontaneous PTB:** weekly IM 17-hydroxyprogesterone caproate (17-OH-P)
  - **If cervical length <25 mm before 24 weeks with prior PTB:** weekly IM 17 -OH-P plus cervical cerclage placement
  - **If cervical length <20 mm before 24 weeks but no prior PTB:** daily vaginal progesterone
- No interventions are shown to have any benefit in cases of twin pregnancy.
- **Progesterone** is used if the patient have history of short cervix from 16 to 36 weeks.

IMP for the exam

		Short Cervix Less than 2 ir 2.5cm: No	Short Cervix Less than 2 ir 2.5cm: Yes
Previous Preterm Birth	No	Nothing needed	**Progesterone**: vaginal daily suppositories
	Yes	**17-OH-progesterone**: IM weekly From week 16 till week 36	**17-OH-progesterone** + **cerclage**

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Screening for cervical length at 12-13w, rescreen at week 16

For short:
previous preterm birth? IM weekly.
No history but short cervix? Vaginal daily.

439 Dr's Notes

- **Preterm labor:** <37 weeks, ≥3 uterine contractions in 30 min and cervical dilation ≥ 2 cm.
- Anything goes wrong in the pregnancy can cause preterm labor.

- **There are two types of preterm delivery:**
  1- spontaneous preterm labor: we don't decide it happened spontaneously
  2- iatrogenic preterm delivery : Ex. if the mother has eclampsia or placenta previa and we decided that she will deliver at 32 weeks.

- **Remember**! Do the ultrasound before the vaginal examination to make sure the placenta at the normal location and there is no rupture of membrane.

- **Why do we give tocolytic?**
  1- have time to give a steroid (dexamethasone) to enhance lung maturity.
  2-to transferred the patient to another hospital.

- At time of labor give magnesium sulfate if <32 weeks,GBS prophylactic & dexamethasone

- GBS given to all preterm labor < 37W, in normal labor 37 and above it is depend on the culture if it is +ve we give, if it is -ve we don't, if unknown , ROM for 18 H or sign of Chorioamnionitis we give it.

- If you give magnesium sulfate You have to check on the patient every six hours to make sure there is no hypotonia or decrease in reflexes or respiratory distress and pulmonary edema if you see a decrease in reflexes stop it immediately.

- **Complication**s **of preterm delivery:** respiratory distress syndrome, intraventricular hemorrhage, necrotizing fasciitis, sepsis all prevented by dexamethasone.
  neurological impairment and cerebral palsy prevented by magnesium sulfate.

- If patients come to you and say that doctor I have preterm delivery history at 30 weeks what should I do in this pregnancy? At 16 weeks we will measure the cervical length > if she has short cervix < 2.5 cm we will give her vaginal progesterone 200mg once we know and continue to 36 W.

- If patients come and say that I have a preterm delivery but she don't has short cervix we give her IM progesterone or vaginal progesterone from 16 -36 weeks.

- I want you to know that progesterone prevents preterm labor in pt with short length you don't need to know about when do we give it or how to diagnose it.

441 Dr's Notes

- **Uterine anomaly like what? Bicornuate, septate....**
- **What does CTG stands for? Cardiotocogram**
- **Why we look for the contractions with the fetal heart?**
    - To check if there is deceleration and it's type
    - To evaluate the cervix (effacement, dilation, position, station, consistency)
- 2 out of 10 patients have true labor when coming to the ER.
- **When the patient comes with abdominal pain and contraction how would you know if it's true labor or Braxton Hicks contractions?**
    - Ask: is it relieved by drinking water? rest? painkillers? Irregular? If yes, then it's not true labour. Cervical os is closed even after 2hs.
    - **Regular means** it's first comes every 15 mins, then every 10mins, then every 5mins...
- **Before doing bimanual examination we do US to assess the baby presentation and the placenta** (must be in the upper portion of the uterus to exclude placenta previa)
- In placenta previa we can do speculum **(ONLY by an expert/senior)** to see if there is blood or not, speculum is just to open the vagina and show you the cervix, you can tell if it's open or not but you can't determine the dilation.
- **GBS: presents in 12-13% of females as normal flora, she might have no symptoms at all, but it might affects the baby, causing PROM or preterm labour (**diagnosis done by special swap, if GBS +ve we have to give them Antibiotic at time of delivery to save the baby from **uveitis, meningitis, septic shock).**
- **Chorioamnionitis: maternal / fetal tachycardia, fever, uterine tenderness.**
- **+ve Fetal fibronectin** means the membrane starts to detach which means the patient is going into labour.
- Bishop score: **above 6** is favorable. Preterm labour: after 24w.
- **Steroids increase the production of surfactant (responsible for lung maturity).** Its production increases with stress of labour at the 3rd trimester, the highest levels at delivery when the baby starts screaming.
- In preterm labour the contractions starts before alveoli gets mature + ventricles still smooth, touching the head can cause bleeding, steroids increases the strength of the ventricles.
- Four 6mg doses of dexamethasone (we use it here) or two 12mg doses of betamethasone
- **All of the to tocolytic administered intravenously except Nifedipine orally.**
- **MgSO4: neural protection and prevent preterm labour.**
- **You should memorize the contraindications and why it's contraindicated.**
- Patient with Myasthenia gravis, is it contraindicated to give her tocolytics? **No! only Magnesium sulfate is contraindicated, we can give her another type.**
- If we give tocolytics during the active phase of 2nd stage we will only increase the risk of infection.
- Previous preterm birth? IM progesterone weekly.
- No history but short cervix? Vaginal progesterone daily.
- **Necrotising enterocolitis:** normal flora opin bowels presents only in term babies. So when preterm babies drink formula milk, bowels gets irritated and inflamed, sometimes perforated, the advise the mothers to breastfeed her preterm baby.
- Retinopathy of prematurity: retina vessels not formed adequately, **that's why premature babies usually wears thick glasses.**
- **Summary of medication timeline:**
    - 24-32: Abx + corticosteriods + MgSO4
    - 32-34: Abx + corticosteroids
    - 34-37: Abx only

Teaching Case

An 18-year-old African-American, G2P0101 (2 pregnancies, 0 term births, 1 preterm birth, 0 losses before 20 weeks "abortions", 1 living child) woman who is 12 weeks pregnant, presents to your prenatal clinic for a new patient visit. Before you walk into the room to see the patient, you look through her records and note that she delivered her last pregnancy just 12 months ago. Beginning at 24 weeks in her previous pregnancy, the patient presented numerous times to Labor and Delivery reporting contractions, and was sent home each time with a diagnosis of "Braxton-Hicks contractions." She eventually presented at 28 weeks gestation and was diagnosed with preterm labor. She delivered at 29 weeks. The neonate's course was complicated by intraventricular hemorrhage and respiratory distress syndrome. The child now appears to have cerebral palsy and chronic lung disease due to bronchopulmonary dysplasia.

Q1: What are the risk factors for preterm labor, and which ones does this patient have?

A. Risk factors of preterm labor:

- Prior preterm birth (PTB)
- Short transvaginal (TV) cervical length (<25 mm)
- PROM
- Multiple gestation
- Polyhydramnios
- Uterine anomaly
- Uterine Tumor
- African American race
- Young patient
- Genitourinary Infections; ex: bacterial vaginosis or streptococcus b
- Low maternal pre-pregnancy weight
- Smoking
- Substance abuse
- Short inter-pregnancy interval
- Vaginal bleeding due to abruption and placenta previa

B. Patient risk factors:

- Young
- African American
- With prior preterm birth
- Short inter-pregnancy interval.

Q2: What characteristics distinguish Braxton-Hicks contractions from true labor contractions?

Braxton-Hicks contractions	True Labor Contractions
Irregular and sporadic contractions	Regular intervals
Painless or mild intensity	Progressive ↑ in frequency and intensity
Not associated with progressive cervical dilation and effacement	Associated with cervical dilation
Relieved by rest, hydration, and/or sedation	Not relieved by sedation

Q3: What should you counsel the patient regarding the signs and symptoms of preterm labor?

Pain:

- Contractions of labor (both True and Braxton-Hicks) are uterine in origin, mimic menstrual cycle, usually associated with low, dull backache and abdominal/pelvic pressure.

Vaginal Discharge:

- Normal labor is associated with vaginal discharge. Once the cervix is dilated due to uterine contractions, a mucus plug is released, and hence, the discharge is mucoid, watery, and slightly stained with blood. If the patient has clear watery discharge, it indicates membrane rupture "Amniotic fluid"

Q4: What recommendations, if any, would you discuss with this patient regarding prevention strategies to reduce the risk of preterm delivery in this pregnancy? To reduce the risk of neurodevelopmental disorders and other morbidity associated with preterm labor in this fetus should she experience preterm labor?

A. Progesterone:

- **Route:** Vaginal or Intramuscular
- **Aim:** Stop contractions and relax the uterus, preventing cervical dilatation (↓risk of preterm labor)
- **Time to Start:** Second trimester (or earlier in case of prior history of PTB)

B. Magnesium Sulfate:

- **Route:** Intravenous
- **Aim:** Reduce risk of cerebral palsy in surviving infants, stop contractions and relax uterine muscles
- **Time to Start:** Between 24-34 weeks <32 weeks

C. Antibiotics:

- **Aim:** prophylactic against Group-B Strep. sepsis in the neonate

D. Antenatal Steroids (Betamethasone or Dexamethasone)

- **Route:** Intramuscular
- **Aim:** Enhance fetal lung maturity, ↓ Respiratory distress syndrome, Intracranial hemorrhage, Necrotizing enterocolitis, death, and risk of necrotizing fasciitis. Use if the mother is diagnosed with PTB, has a prior history of PTB, or at risk of PTB
- **Time to Start:** Between 24 - 34 weeks

Q5: If the patient does experience PTL in this pregnancy, what recommendations would you make regarding treatment and management?

A. Assessment:

- Fetal fibronectin testing (negative) and cervical length (greater than 2.5 cm) have good negative predictive value in deciding which patients do not require treatment for preterm labor. Fetal fibronectin testing is a chemical test where you take the cervical discharge or mucus and check: if it is positive = increased risk of premature birth ,negative = low risk.

B. Administration:

- Delay the delivery (buy more time) until steroids can take action with tocolytic medication (uterine relaxers) for a maximum period of 7 days.

The risks of tocolytics include:

- **Magnesium Sulfate:**
  - Hypotonia
  - Maternal Flushing
  - Decreased reflexes
  - Muscle weakness
  - Pulmonary edema
  - Fetal lethargy
  - Fetal hypotonia
  - Fetal respiratory distress (in large doses)
  - Fetal bone abnormalities (if used > 7 days)
- **Nifedipine:** Maternal hypotension
- **Indomethacin:**
  - Maternal nausea
  - Esophageal reflux
  - Gastritis
  - Platelet dysfunction
  - Fetal preterm closure of ductus arteriosus (with >48 hour use)
- **Beta-mimetics** (most commonly used agent):
  - Maternal tachycardia
  - Hypotension
  - Tremor
  - Shortness of breath
  - Chest discomfort
  - Pulmonary edema
  - Hypokalemia
  - Hyperglycemia
  - Fetal tachycardia (continuous CTG)

Q6: What are the potential adverse outcomes of preterm birth for the fetus?

- Respiratory distress syndrome (most common) prevent it by dexa.
- Intraventricular hemorrhage prevent it by dexa.
- Bronchopulmonary dysplasia (especially those who are born too prematurely) prevent it by dexa.
- Necrotizing enterocolitis prevent it by dexa.
- Sepsis prevent it by dexa + GBS prophylaxis penicillin G.
- Neurological impairment prevent it by magnesium sulfate.
- Seizures prevent it by magnesium sulfate.
- Cerebral palsy prevent it by magnesium sulfate.

Reference

Preterm Labor

Worldwide, preterm labor and delivery are major causes of perinatal morbidity and mortality. **Although fewer than 12% of all infants born in the United States are preterm, their contribution to neonatal morbidity and mortality ranges from 50-70%.** The medical and economic impact of preterm delivery is significant. Major goals of obstetric care should be to reduce the incidence of the condition and to increase the gestational age of infants whose preterm births are unavoidable.

DEFINITION AND INCIDENCE

Preterm birth (PTB) is usually defined as one occurring after 20 weeks and before 37 completed weeks of gestation. Labor that occurs between these gestational ages is defined as preterm labor. Internationally, the lower boundary defining preterm birth varies between 20 and 24 weeks.

Preterm births in the United States increased from 9.8% in 1981 to 12.7% in 2005; however, in the past 6 years, the rate has declined for the seventh straight year to 11.4%. Between 1988 and 2004, the mortality rate for white infants declined by 55% to 5.7 infant deaths per 1000 live births and the mortality rate for black infants declined by 45% to 13.6. In the past 10 years the decline in infant mortality for both races has been less than anticipated. **Because prematurity is the leading cause of infant mortality, the prevention of prematurity has become a high priority.**

ETIOLOGY AND RISK FACTORS

The causes of preterm birth and their estimated frequencies are listed in Table 12-1. **Private patients have a much higher proportion of spontaneous preterm labor, whereas black patients in public institutions have a higher proportion of deliveries due to preterm premature rupture of membranes (PPROM).**

TABLE 12-1

PRIMARY CAUSES OF PRETERM BIRTH AND THEIR ESTIMATED FREQUENCY

Cause	Frequency (%)
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Antepartum hemorrhage	5-6
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Attempts have been made to define further the spontaneous preterm labor subgroups. Some experts now believe this may be caused by undiagnosed conditions of poor placental implantation, ascending infections via the vagina, or immunologic rejection of uterine and cervical origin. **Recently, genetic thrombophilias have been shown to account for a significant proportion of the uteroplacental problems leading to IUGR and preeclampsia,** the two major reasons for the early induction of labor to avoid fetal death. In the past 10 years, closer surveillance of high risk pregnancies has led to earlier delivery and an increase in the rate of late preterm deliveries (between 34 and 37 weeks), a major contribution to the continued high rate of preterm birth. The decline in preterm birth rate over the past 7 years is thought to be related to the reduced incidence of late preterm birth deliveries.

More women are postponing childbirth as a lifestyle choice, but this is associated with a greater risk of infertility. These women then require assisted reproductive technologies (ARTs) to become pregnant. These technologies are associated with the risk of multiple gestations and the associated increased risks of poor fetal growth and preterm birth. A variety of socioeconomic, psychosocial, and medical conditions have been found to carry an increased risk of preterm delivery in women who postpone childbearing.

Socioeconomic Factors

In the United States, the incidence of preterm deliveries in the black population is twice as high as that in the white population. This factor cannot be viewed as a single entity but probably encompasses other characteristics of the population, such as poor access to, and procurement of, antenatal care, high stress levels, poor nutritional status, and the possibility of genetic differences. In the past 6 years there has been an increase in the incidence of poverty and obesity, which may contribute to the persistence of high levels of preterm birth.

Obstetric, Medical, and Environmental Factors

1. **Recurrent preterm birth:** When one preterm birth has occurred, the relative risk of preterm delivery in the next pregnancy is 3.9, which increases to 6.5 with two previous preterm deliveries.
2. **Second-trimester abortions:** The cause of second-trimester abortions when the fetus is normal is likely to have the same cause as preterm labor (PTL) after 20 weeks. Therefore, these early pregnancy losses are associated with an increased risk for subsequent preterm delivery, especially if a previous preterm birth has also occurred. The risk associated with induced first-trimester abortions is controversial, because they are more likely associated with malformed fetuses that may not have aborted spontaneously. However, if there are repeated first-trimester spontaneous abortions, there is an increased risk of spontaneous loss of a normal fetus because of immunological causes that are poorly understood. Other obstetric factors include multiple gestation and polyhydramnios.
3. **Medical factors:** The major medical factors are hypertension, diabetes, obesity, and genital tract infection. Other factors include bleeding in the first trimester, urinary tract infections, uterine anomalies, and incompetent cervix.
4. **Environmental and behavior factors:** Smoking during pregnancy is associated with an increased risk of preterm birth. Smoking cessation should be considered in any preventative program for preterm birth. Recently, attention has been directed toward maternal employment, physical activity, nutritional status stress, and anxiety as major risk factors for preterm birth. In addition, several papers have associated vitamin D deficiency with a greater risk of preterm birth, preeclampsia, and IUGR.

PATHWAYS THOUGHT TO CAUSE PRETERM BIRTH:

1. Infection (cervical-vaginal-urinary)
2. Placental-vascular
3. Psychosocial stress and work strain (fatigue)
4. Uterine stretch (multiple gestations)

Infection-Cervical Pathway

Bacterial vaginosis has been shown to be associated with preterm delivery, independent of other recognized risk factors. **Treatment of bacterial vaginosis has reduced the incidence of preterm delivery. For many years, it has been known that treatment of asymptomatic and clinical cystitis is associated with a reduced incidence of PTB.** In addition, treating women in preterm labor with antibiotics significantly prolongs the time from the onset of treatment to delivery, compared with that in patients who do not receive antibiotics. Thus, addressing the issue of these relatively asymptomatic infections is an important strategy for preventing preterm birth.

There is a link between vaginal-cervical infections and progressive changes in the cervical length, as measured by vaginal ultrasonography. The relative risk of preterm birth increases significantly from 2.4 for a cervical length of 3.5 cm (50th percentile) to 6.2 for a length of 2.5 cm (10th percentile). **Short cervices appear to be more common in women who have had prior preterm births and pregnancy terminations.**

The most recent test to be developed is cervical and vaginal fetal fibronectin. This substance is a basement membrane protein produced by the fetal membranes. When the fetal membranes are disrupted, as with repetitive uterine activity, and/or in the presence of infection, shortening of the cervix can occur. In the presence of these changes, fibronectin (a protein substance) is secreted into the vagina and can be tested. **A positive fetal fibronectin test at 22 to 24 weeks predicts more than half of the spontaneous preterm births that occur before 28 weeks.** A positive test for fetal fibronectin is significantly associated with a short cervix, vaginal infections, and uterine activity. A negative test is the best predictor of a low risk of preterm delivery.

Placental-Vascular Pathway

The placental-vascular pathway begins early in pregnancy at the time of implantation, when there are important changes taking place at the placental/decidual/myometrial interface. Initially, there are important immunologic changes, with a switch from a Th-1 (helper cell) type of immunity, which may be embryotoxic, to a Th-2 antibody profile, in which blocking antibody production is thought to prevent rejection. At the same time, the trophoblasts are invading the spiral arteries of the decidua and myometrium, assuring that a low resistance vascular connection is established. **All three conditions associated with preterm delivery (spontaneous, PROM, and IUGR) are associated with failure of the trophoblast to properly invade the spinal arteries.** Poor trophoblastic invasion may be caused by placental factors or maternal abnormalities secondary to atherosclerosis. Alterations in both of these early changes are thought to play an important role in the pathophysiology of poor fetal growth, an important component of preterm birth (indicated and spontaneous), fetal growth restriction, and preeclampsia.

The placenta is also an important source of progesterone production that plays an important role in the immune system and in the maintenance of uterine relaxation. The altered placental progesterone production in women at risk of preterm birth is thought to be secondary to placental hormonal dysregulation. Both 17-OH progesterone and vaginal progesterone play an important role in the prevention of preterm birth.

Stress-Strain Pathway

Both mental (cognitive) and work-related stress and strain are postulated to initiate a stress response that increases release of cortisol and catecholamines. The biochemical response to stress is important for the maintenance of metabolic regulation. However, cortisol from the adrenal gland initiates early placental corticotrophin-releasing hormone (CRH) gene expression, and elevated levels of CRH are known to initiate labor at term. Catecholamines released during the stress response not only affect blood flow to the uteroplacental unit, but also cause uterine contractions (norepinephrine). Poor nutrition in the form of reduced calories and/or abnormal patterns of intake (fasting) are known stressors and have been associated with a significantly increased risk of preterm birth. **In support of the stress pathway are the studies that have shown that the rate of change of CRH, a mediator of the stress response, increases significantly in the weeks before the onset of preterm labor. Thus, too much stress (chronic stress) is thought to be toxic and may cause preterm labor.** Stress reduction and psychosocial support are the only current interventions that can be applied to this pathway. Meta-analyses have suggested that psychosocial support via networking between women's social groups can decrease the risk of preterm birth.

Uterine Stretch Pathway

Uterine stretch as a result of increasing volume during normal and abnormal gestations is an important physiological mechanism that facilitates the process of emptying the uterus. In normal pregnancy, the hormone **parathyroid-related protein (PTrP)** plays an important role in relaxing the myometrial tissues, but when stretch exceeds certain limits (e.g., multiple gestations, fetal macrosomia, and polyhydramnios), PTrP fails to keep the uterus relaxed and labor begins. This pathway is common in patients with **polyhydramnios** and those with **multiple gestations,** both of which have an increased risk of preterm birth.

PREVENTION OF PRETERM BIRTH

The ideal time to assess risk factors for premature labor and PTB is before conception. This allows time to identify problems and take measures to mitigate any risk. Unfortunately, very few women are seen before pregnancy for the type of counseling and intervention that would be necessary (see Chapter 7) and it is usually at the first prenatal visit that these measures are initiated. **The important risk factors for PTB are a history of previous PTB, a family history of PTB and child abuse, smoking (including second hand), a history of recurrent early pregnancy losses, previous cervical surgery, obesity, substance abuse, and medical conditions such as hypertension and diabetes.**

For all women, but particularly those who are at high risk for PTB, medical conditions should be managed and appropriate supplementation of folic acid (4 mg/day) and vitamin D (2000 to 3000 IU/day) should be initiated in early pregnancy, in addition to prenatal vitamins. A probiotic supplement should be considered to improve the gut biome. The length of the cervix should be a component of the ultrasonic study at 18 to 20 weeks. **Women with a short cervix (between 10 and 20 mm) should receive vaginal progesterone 200 mg daily from 19 to 20 weeks until 36 weeks.** For women with a history of PTB, 250 mg intramuscular 17OH progesterone caproate weekly, until 36 weeks, or vaginal progesterone, 200 mg daily from 16 to 36 weeks should be initiated.

DIAGNOSIS AND MANAGEMENT OF PRETERM LABOR

The diagnosis of preterm labor between 20 and 37 weeks is based on the following criteria in patients with ruptured or intact membranes: (1) **documented uterine contractions** (4 per 20 minutes or 8 per 60 minutes) and (2) **documented cervical change** (cervical effacement of 80% or cervical dilation of 2 cm or more). Uterine contractions are not a good predictor of preterm labor, but cervical changes are.

Provided that membranes are not ruptured and there is no contraindication to a vaginal examination (e.g., placenta previa), **an initial assessment must be done to ascertain cervical length and dilation and the station and nature of the presenting part.** The patient should also be evaluated for the presence of any underlying correctable problem, such as a urinary tract or vaginal infection. She should be placed in the lateral decubitus position to take the uterine weight off the great vessels, monitored for the presence and frequency of uterine activity, and reexamined for evidence of cervical change after an appropriate interval, unless the preceding criteria for preterm labor have already been met. **During the period of observation, either oral or parenteral hydration (5% dextrose) should be initiated.** Clear liquids of caloric value should be considered. Fasting is not healthy during this phase of management.

With adequate hydration and bed rest, uterine contractions cease in approximately 20% of patients. These patients, however, remain at high risk for recurrent preterm labor.

Because of the role of cervical colonization and vaginal infection in the etiology of preterm labor and PROM, **cultures should be taken for group B *Streptococcus.*** Other organisms that may be important are *Ureaplasma, Mycoplasma,* and *Gardnerella vaginalis.* The latter is associated with bacterial vaginosis, a diagnosis that can be made by the presence of three of four clinical signs (vaginal pH > 4.5, amine odor after addition of a few drops of 10% potassium hydroxide [KOH] on a glass slide, the presence of clue cells, and the presence of a milky discharge).

Antibiotics should be administered to patients who are in preterm labor. For patients who are not allergic to penicillin, a 7-day course of ampicillin and erythromycin may be given. Those allergic to penicillin may be given clindamycin.

Once the diagnosis of preterm labor has been made, the following laboratory tests should be obtained: complete blood cell count, random blood glucose level, serum electrolyte levels, urinalysis, and urine culture and sensitivity. **An ultrasonic examination of the fetus should be performed to assess fetal weight, document presentation, assess cervical length, and rule out the presence of any accompanying congenital malformation.** The test may also detect an underlying etiologic factor, such as twin pregnancy or uterine anomaly.

If the patient does not respond to bed rest and hydration, tocolytic therapy should be instituted, provided that there are no contraindications. Measures implemented at 28 weeks should be more aggressive than those initiated at 35 weeks. Similarly, a patient with advanced cervical dilation on admission requires more aggressive management than one whose cervix is closed and minimally effaced.

UTERINE TOCOLYTIC THERAPY

It is assumed that physiologic events leading to the initiation of labor also occur in preterm labor. The pharmacologic agents presently being used all seem to inhibit the availability of calcium ions, but they may also exert a number of other effects. The agents currently used and their dosages are presented in Box 12-1.

Magnesium Sulfate

In the United States, magnesium sulfate is frequently the drug of choice for initiating tocolytic therapy. Magnesium acts at the cellular level by competing with calcium for entry into the cell at the time of depolarization. Successful competition results in an effective decrease of intracellular calcium ions, resulting in myometrial relaxation.

BOX 12-1

UTERINE TOCOLYTIC AGENTS

Magnesium Sulfate

Solution: Initial solution contains 6 g (12 mL of 50% $MgSO_4$) in 100 mL of 5% dextrose; maintenance solution contains 10 g (20 mL of 50% $MgSO_4$) in 500 mL of 5% dextrose
Initial dose: 6 g over 15 to 20 min, parenterally
Titrating dose: 2 g/hr until contractions cease; follow serum levels (5-7 mg/dL); maximal dose, 4 g/hr
Maintenance dose: Maintain dose for 12 hr, then 1 g/hr for 24 to 48 hr; consider switching to nifedipine (see below)

Nifedipine

Preparation: Oral gelatin capsules of 10 or 20 mg
Loading dose: 30 mg; if contractions persist after 90 min, give an additional 20 mg (second dose); if labor is suppressed, a maintenance dose of 20 mg is given orally every 6 hr for 24 hr and then every 8 hr for another 24 hr
Failure: If contractions persist 60 min after the second dose, treatment should be considered a failure

Prostaglandin Synthetase Inhibitors

Short-term use only

Although magnesium levels required for tocolysis have not been critically evaluated, it appears that the levels needed may be higher than those required for prevention of eclampsia. Levels from 5.5 to 7.0 mg/dL appear to be appropriate. These can be achieved using the dosage regimen outlined in Box 12-1. **After the loading dose is given, a continuous infusion is maintained, and plasma levels should be determined until therapeutic levels have been reached.** The drug should be continued at therapeutic levels until contractions cease unless the labor progresses. Because magnesium is excreted via the kidneys, adjustments must be made in patients with an abnormal creatinine clearance. **Once successful tocolysis has been achieved, the infusion should be continued for at least 12 hours. The infusion rate may then be weaned over 2 to 4 hours and then discontinued.** In very high risk patients (advanced cervical dilation or continued labor in very low birth weight cases), the infusion may be continued until the fetus has been exposed to glucocorticoids to enhance lung maturity.

A common minor side effect is a feeling of warmth and flushing on first administration. Respiratory depression is seen at magnesium levels of 12 to 15 mg/dL, and **cardiac conduction defects and arrest** are seen at higher levels.

In the fetus, plasma magnesium levels approach those of the mother, and a low plasma calcium level may also be demonstrated. **The neonate may show some loss of muscle tone and drowsiness, resulting in a lower Apgar score.** These effects are prolonged in the preterm neonate because of the decrease in renal clearance.

Long-term parenteral magnesium therapy has been used for control of preterm labor in selected patients. An important side effect seems to be loss of calcium, and it may be important in such patients to institute calcium therapy on a prophylactic basis. Because vitamin D deficiency has been associated with the risk of premature labor, vitamin D supplementation should be considered because vitamin D is required for adequate mobilization of calcium from the skeleton.

Nifedipine

Nifedipine as an oral agent is very effective in suppressing preterm labor with minimal maternal and fetal side effects. It works by inhibiting the slow, inward current of calcium ions during the second phase of the action potential of uterine smooth muscle cells **and may gradually replace intravenous magnesium sulfate.** The only side effects are headache, cutaneous flushing, hypotension, and tachycardia. The latter two side effects can be partially avoided by making certain the patient is well hydrated and by the use of support stockings, such as thromboembolism-deterrent (TED) hose, to prevent pooling of blood in the lower extremities.

Reference

Prostaglandin Synthetase Inhibitors

Prostaglandins induce myometrial contractions at all stages of gestation, both in vivo and in vitro. Because prostaglandins are locally synthesized and possess a relatively short half-life, prevention of their synthesis within the uterus could inhibit labor. **These agents are used on a short-term basis** in circumstances where prostaglandin production may be the inciting factor, as may occur in the presence of uterine fibroids. In the United States **indomethacin is the most commonly used prostaglandin inhibitor; it can be administered both orally and rectally, with some slight delay in absorption from rectal administration as compared with the oral route.** Peak serum levels of indomethacin occur 1.5 to 2 hours after oral administration. Excretion of the intact drug occurs in maternal urine. It can result in oligohydramnios and premature closure of the fetal ductus arteriosus, which in turn may lead to neonatal pulmonary hypertension and cardiac failure. In addition, **indomethacin decreases fetal renal function, and indomethacin-exposed infants have a greater risk of necrotizing enterocolitis, intracranial hemorrhage, and patent ductus arteriosus.** Short-term use may be acceptable, but if patients are given indomethacin, the fetus should be evaluated with ultrasonography for ductus arteriosus flow.

Combined therapy with nifedipine and prostaglandin synthetase inhibitors is currently being used in Australia, Canada, and Europe.

Oxytocin Receptor Antagonists

Atosiban was the first oxytocin receptor antagonist developed. It binds to receptors in the myometrium and other gestational tissues, preventing the oxytocin-induced increase in inositol triphosphate. The latter is the messenger that increases intracellular calcium, and causes myometrial contractions and up-regulation of prostaglandin production. **These agents are not approved for use in the United States.**

Efficacy of Tocolytic Therapy

Although the advent of tocolytic agents has failed to decrease preterm births in large population studies, their use has improved neonatal survival, decreased respiratory distress syndrome (RDS), and increased the birth weight of infants. The benefit of measures to postpone delivery beyond 34 weeks is under investigation, with the thought that the longer the fetus remains in utero the better the outcome.

Antibiotic Therapy

A number of studies have advocated the use of antibiotic prophylaxis in patients with preterm labor. Such patients may have a higher incidence of **subclinical chorioamnionitis** than previously thought.

Diagnostic amniocentesis in patients with idiopathic preterm labor has identified about 15% whose amniotic cavity is colonized with pathogens. It is reasonable to assume that a proportion of the remainder will have occult bacteria in the decidual cell space between the chorion and the myometrium. **The use of prophylactic antibiotics in women with preterm labor may prevent progression from a subclinical infection to clinical amnionitis.**

Contraindications to Tocolytic Therapy

Contraindications include **severe preeclampsia, severe bleeding from placenta previa or abruptio placentae, chorioamnionitis, IUGR, fetal anomalies incompatible with life, and fetal demise.** Because of the low success rate, advanced cervical dilation may also preclude tocolytic therapy, although therapy may delay delivery sufficiently for glucocorticoid administration to accelerate fetal lung maturity. Management of patients should be individualized, and even if the patient's cervix is dilated to 6 cm and infrequent contractions are occurring, it is advisable to employ tocolytics and to administer glucocorticoid therapy.

USE OF GLUCOCORTICOIDS FOR FETAL PULMONARY MATURATION

Antenatal corticosteroid therapy for fetal pulmonary maturation reduces mortality and the incidence of RDS and intraventricular hemorrhage (IVH) in preterm infants. These benefits extend to a broad range of gestational ages (24 to 34 weeks) and are not limited by gender or race. **Treatment consists of 2 doses of 12 mg of betamethasone, given intramuscularly 24 hours apart, or 4 doses of 6 mg of dexamethasone given intramuscularly 12 hours apart.** Optimal benefit begins 24 hours after initiation of therapy and lasts 7 days. Treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal mortality secondary to respiratory distress syndrome and intraventricular hemorrhage, so they should be given unless immediate delivery is anticipated.

LABOR AND DELIVERY OF THE PRETERM INFANT

A certain number of patients will not respond to tocolytic therapy. The goal in these patients should be to conduct both labor and delivery in an optimal manner so as not to contribute to the morbidity or mortality of the preterm infant. All parameters for assessing gestational age and fetal weight must be considered. **With modern neonatal care, the lower limit of potential viability is 24 weeks or 500 g, although these limits vary with the expertise of the neonatal intensive care unit.**

Fetal heart rate patterns characterized as Category II (Intermediate/possibly Early Dysregulation; see Boxes 9-1 and 9-2) that are relatively innocuous in the term fetus may indicate a more ominous outcome for the preterm fetus. The clinician should not wait until

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Good Luck!

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