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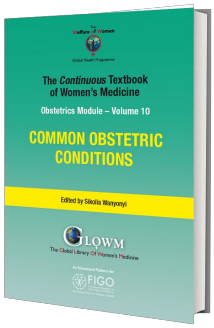

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Chapter

Preterm Labor

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INTRODUCTION

Preterm labor is the onset of labor before 37 weeks' gestation. This accounts for about 5–18% of births worldwide and the highest proportion of perinatal mortality following preterm birth. There are also significant long-term health consequences for survivors of preterm birth. Preterm birth may be a result of preterm labor, premature preterm rupture of membranes (PPROM) or medically indicated preterm delivery for maternal or neonatal reasons. Neonatal and long-term risks depend upon the severity of prematurity and are inversely proportional to the gestational age at birth. Gestation at birth is categorized as extreme prematurity (<28 weeks' gestation), severe prematurity (28–32 weeks' gestation), moderate prematurity (32–34 weeks' gestation) and near term (34–36 weeks' gestation). Perinatal mortality increases markedly as gestational age and birth weight decline.

EPIDEMIOLOGY

Despite advances in neonatal care, perinatal mortality and morbidity appears to have remained stable over the past 40 years in preterm born neonates globally. This may be due to increasing access to assisted reproductive technologies (ART) and an increasing proportion of extremely premature deliveries. There is also an increasing proportion of pregnant women with advanced maternal age, high body mass index and medical conditions such hypertension and diabetes especially in developed countries. Due to variation in the lower cut-off gestation for preterm birth and miscarriage, previous studies have reported varied proportions of preterm labor and birth depending on geographical location.

Although the proportion of preterm labor at less than 28 weeks is low, accounting for about 5% of all preterm births perinatal, childhood and long-term complications are disproportionately high in this gestational age band.

Neonatal survival following preterm birth is higher in developed countries compared to developing countries. In developing countries half of all babies born at or before 32 weeks' gestation die, whereas nearly all survive in developed countries. It is estimated that 15 million babies are born preterm worldwide with more than one million dying of prematurity complications. Globally, ten countries with the highest number of preterm births are developing countries except the USA.[54]

RISK FACTORS

Seventy five per cent of preterm births happen following spontaneous preterm labor and PPROM. Preterm labor is considered to be quite similar to term labor in its physiological mechanisms that include regular uterine contractions, progressive cervical dilation and membrane rupture. Whereas the mechanisms of labor may be similar at both term and preterm, the former is physiological and the latter a pathological activation of labor mechanisms.

Not all preterm labor is associated with identifiable antecedent risk factors, and this may differ between high-income countries and low- and middle-income countries. Table 1 summarizes known risk factors for preterm labor and PPROM.

Epidemiological evidence consistently shows that Black women compared to their Caucasian counterparts are at increased risk of preterm birth with an even higher risk of severe preterm birth in the USA.[1] It is not completely understood why this is the case; however, it is postulated that Black women are likely to be more socially deprived and at higher risk of psychological morbidity and stress. In addition, the prevalence of bacterial vaginosis appears to be higher in Black than Caucasian women.[2,3,4] These factors are associated with a higher risk for preterm birth; however, it is difficult to disentangle the actual reasons for the disparity due to confounding factors. Clearly, there is no biological explanation as studies have reported the risk of preterm birth increases with the duration of time spent in the USA by foreign-born women.

The single most significant risk factor for preterm birth is a history of previous preterm birth with recurrences often occurring at the same gestational age.[5] The risk being inversely proportional to the gestation at which the previous birth occurred. It is estimated that the risk for subsequent preterm birth may be 2.5-fold higher following a previous preterm birth. Whereas persistent factors have not been elucidated that may account for this residual risk, it forms the basis for cervical length measurement during pregnancy.

Women at extremes of maternal age have higher rates of preterm birth, this could be due to younger adults being physiologically immature or impacting socioeconomic factors, whilst older mothers have a higher prevalence of pre-existing conditions and obesity.[6]

The proportion of multiple pregnancies spontaneously conceived remains low, however, with advent of ART, pregnancies following ART are increasingly becoming common even in developing countries. Pregnancies conceived by ART are at a higher risk of preterm birth even if they result in a singleton gestation.[7] The highest risk follows multiple embryo transfer, even though there seems to be an increase in the risk of monozygotic multifetal pregnancy with blastocyst or embryo manipulation techniques. Twins carry a substantial risk of preterm birth of nearly 60% and account for 15–20% of all preterm births. More than three-quarters of higher order multiple pregnancies will be born preterm, more likely in the severe preterm gestational age bracket.

The majority of these preterm births will be a result of spontaneous preterm labor. Uterine over-distension is the mechanism behind preterm labor initiation. Moreover, twin pregnancies are likely to be complicated by maternal conditions such as hypertension, pre-eclampsia and gestational diabetes that require iatrogenic preterm delivery.

Generally, the interval for a subsequent pregnancy is likely to be longer following a term pregnancy with a good outcome. Women with a shorter inter-pregnancy interval of <6 months have a two-fold increased risk of preterm birth.[8] The mechanism for this increased risk is unknown, though it could be due to a higher risk of preterm birth in the preceding pregnancy. Women who conceive using ART may be in haste to conceive following delivery so they can complete their families sooner due to a variety of reasons, not the least being maternal age.

Social factors such as maternal smoking and alcohol consumption are associated with adverse pregnancy outcomes. In the USA, up to 15% of women who become pregnant while smoking will continue to smoke throughout pregnancy. There are many chemical compounds found in tobacco smoke though no specific chemical has been identified as responsible for how the 2-fold increased risk of preterm birth is conferred. Women who smoke or use substances are also at

increased risk of other factors such as social deprivation, psychological disturbances or extremes of body mass index, confounders which are difficult to separate from the attributable risk from the substance abuse.[9,10]

Early pregnancy bleeding is not uncommon and is associated with increased risk of preterm labor, PPROM, placental abruption and severe pre-eclampsia.[11] In addition, women with placental abruption, previa or who experience unexplained vaginal bleeding after the first trimester have a higher risk of preterm delivery.

Cervical surgery and cervical irregularities also contribute greatly to the increased risk of preterm labor, whilst cervical length measurement has become an important surveillance method in these women. Surgeries to the cervix include cold knife conization and loop electrosurgical excision procedures. Women with a short cervix, as measured by transvaginal ultrasound between 16 and 28 weeks' gestation, have an inversely related to the risk of preterm birth in both singletons and twins. Furthermore, cervical dilation of >1 cm before 24 weeks' gestation is associated with an increased risk of preterm birth. Congenital uterine abnormalities can affect the cervix and/or the uterine corpus with the risk of preterm birth of up to 25–50% depending on the specific abnormality. The presence of large (>5–6 cm) or multiple uterine leiomyomas is an important risk factor for preterm birth with those with a submucosal location further contributing to pregnancy loss.[12,13]

Infections in pregnancy have been associated with preterm labor and birth. These include asymptomatic bacteriuria and genital tract infections. Studies are unclear on whether asymptomatic bacteriuria is an independent risk factor for preterm birth;[14] however, practice guidelines suggest a first trimester urine culture be performed on all pregnant women with antenatal screening performed on those at high risk for asymptomatic bacteriuria. Colonization of the genital tract with group B streptococci (GBS), *Chlamydia trachomatis*, bacterial vaginosis (BV), *Neisseria gonorrhoea*, syphilis, *Trichomonas vaginalis*, *Ureaplasma* species, and unencapsulated *Haemophilus influenza* have all been associated with an increased risk of preterm birth.

Table 1 Risk factors for preterm birth.

Maternal	Pregnancy characteristics
Black race	Previous preterm birth
<17 or >35 years of age	Assisted conception, e.g. IVF
Psychological stress	Multiple pregnancy
Low socioeconomic status	PPROM
Behavior: smoking/alcohol/cocaine/heroin	Antepartum hemorrhage
Low pre-pregnancy BMI	Polyhydramnios
Cervical conization or multiple D&Es	Interpregnancy interval <6 months
Uterine anomalies	Medical conditions: hypertension, diabetes, thyroid disease, asthma
	Infections in pregnancy

PPROM, preterm premature rupture of the membranes; BMI, body mass index.

PATHOPHYSIOLOGY OF PRETERM LABOR

The mechanisms of labor are similar at both term and preterm; however, the former is physiological and the latter a pathological activation of labor mechanisms. Preterm labor likely occurs when local uterine factors are prematurely stimulated or there is a premature withdrawal of the factors that maintain uterine quiescence.

During pregnancy, uterine quiescence is maintained by progesterone hormone acting to reduce up regulation of the contraction associated proteins and prostaglandin activity, hence inhibition of uterine activity and cervical changes. It is

not known how labor is initiated in human term pregnancy. Similarly, the exact mechanisms of the onset of preterm labor are unknown, though it is thought to be a heterogeneous process. Complex mechanisms converge and lead to cervical ripening and dilation, membrane activation and rupture, and increased uterine contractility ending as the final process of labor both in term and preterm pregnancy.

Four major factors leading to preterm labor are intrauterine infection, decidual hemorrhage, excessive uterine stretch and maternal or fetal stress. This pathophysiological construct of uterine distension, placental ischemia and chorio-decidual activation or inflammation has been proposed as the trigger of preterm labor. Central to this is an inflammatory process that results in prostaglandin release. Prostaglandins are well known in the propagation mechanisms in the process of labor. Pathological activation of these pathways manifests clinically in the form of cervical insufficiency, preterm uterine contractions or PPROM.

A significant amount of scientific work demonstrates that infection underlies preterm labor in nearly 40% of cases. The amniotic fluid environment is considered sterile with less than 1% of women at term having bacteria in the amniotic fluid. Interestingly, women who had bacteria (*Mycoplasma hominis* and *Ureaplasma urealyticum*) incidentally isolated from the amniotic fluid during amniocentesis went on to have preterm birth. The earlier the gestational age at preterm birth, the more likely that microbial invasion of the amniotic cavity is present.

Evidence for infection causing preterm birth is strengthened by the increased level of inflammatory markers present. These protect the host against infection but are similar to mediators that trigger parturition thus in the setting of infection, the onset of preterm labor is likely a host defence mechanism.

Maternal BV is a consistently reported risk factor for spontaneous preterm delivery, yet treatment of BV does not reliably prevent preterm birth in women with BV.[15] Emerging evidence has shown that pregnancy alters the vaginal microbiome in favor of *Lactobacillus* spp. compared to BV organisms with the exception of BV-associated bacterium 1 (BVAB1) which has been found to be more prevalent in African women. This gene–environment interaction contributes to the manifestation of preterm labor.

After inflammation, the most common abnormality seen in placental pathology from preterm births is vascular lesions, both in the maternal and fetal circulation.[16] Uteroplacental ischemia caused by failure of physiological transformation of maternal spiral arteries (similar to the pathogenesis of pre-eclampsia and intrauterine growth restriction) has been shown in women with preterm labor. Furthermore, abnormal uterine artery Doppler velocimetry has been reported in women with apparently idiopathic preterm labor. The decidua is a rich source of tissue factor which is the principal initiator of coagulation and thrombin activation, decidual necrosis and hemorrhage can activate labor mechanisms through the production of thrombin which stimulates uterine contractility in a dose–dependent manner. This accounts for the clinical association of vaginal bleeding and hemorrhage with preterm labor and PPROM.[17,18]

Uterine over distension linked to multiple gestation, polyhydramnios, etc. is a well described risk factor for preterm birth. The stretch effect on the myometrium induces the formation of gap junctions, upregulation of oxytocin receptors, increased production of inflammatory cytokines and prostaglandins, and myosin light chain kinase, culminating in uterine contractions and cervical dilation.[19] Stretch can also affect the fetal membranes causing an increase in production of collagenase, interleukin-8 and prostaglandin E_2 which contribute to membrane rupture.

Premature activation of the maternal or fetal hypothalamus–pituitary–adrenal (HPA) axis related to stress is the fourth major factor in the pathogenesis of preterm birth. The main fetal stressor leading to preterm birth is uteroplacental ischemia,[20,21] this is due to increased corticotropin-releasing hormone,[22] binding to the ligand binding site on the progesterone receptor[23] and increased release of fetal pituitary adrenocorticotropic hormone.[24] Severe maternal psychosocial stress has also been implicated in the activation of the maternal HPA axis with worsening of symptoms increasing the risk of preterm birth.[25,26,27]

Pathological cervical change leading to a sonographic short cervix and subsequent preterm birth results from activation of both the hemorrhagic and the inflammatory pathways, whilst maintaining myometrial quiescence resulting in cervical changes without preterm labor. Cerclage may be helpful in selected instances.

Fetal fibronectin (fFN) is an extracellular matrix protein that is present at the decidual–chorionic interface. Dissolution of the extracellular fibronectins is thought to be responsible for the process that allows the membranes to separate from the decidua after birth. Detection of fFN between 22 and 37 weeks' gestation is evidence of disruption of the decidual–

chorionic interface and is associated with an increased risk of preterm labor.[28] Disruption can occur due to infection, inflammation, abruption or uterine contractions.

CLINICAL FINDINGS

True labor is defined by regular contractions plus cervical change whether this is at term or preterm. It is important to distinguish this from false labor where contractions do not result in cervical change. Symptoms include:

1. Abdominal cramping;
2. Contractions (these increase in both frequency and duration in true labor);
3. Pressure sensation in the pelvis;
4. Vaginal discharge, e.g. mucus plug or bloody show.

Any acute conditions that threaten the health of the mother and the fetus should be assessed and may mandate delivery, e.g. acute pyelonephritis, asthma, pneumonia, trauma, severe pre-eclampsia, placental abruption or previa and chorioamnionitis. Fetal compromise may be acute and manifest as an abnormal cardiotocogram or chronic manifesting as fetal growth restriction or oligohydramnios.

DIAGNOSTIC EVALUATION

This is performed on the labor unit:

1. History and assessment:
    a. Review of past and present obstetric history – looking for any risk factors for preterm birth;
    b. Ensure correct assessment of gestational age;
    c. Evaluate for clinical signs of labor;
    d. Take maternal vital signs;
    e. Examine uterus for firmness, tenderness, fetal size and position;
    f. Perform a cardiotocogram;
    g. Assess maternal contractions in terms of frequency, intensity and duration.
2. Speculum examination:
    a. Estimate cervical dilation (≥3 cm supports preterm labor);
    b. Assess per vaginal bleeding if any;
    c. Assess for PPROM:
        i. Pooling of amniotic fluid observed;
        ii. If pooling is not observed, perform an insulin-like growth factor binding protein-1 or placental alpha-microglobulin-1 test of vaginal fluid;
        iii. Do not use nitrazine to diagnose PPROM;
    d. Swab cervicovaginal fluid for fetal fibronectin (fFN) testing;
    e. Culture swab for chlamydia/gonorrhea (cervix) and group B streptococcus (rectovaginal).
3. Digital cervical examination:
    a. Assessment of cervical dilation;
    b. Perform if placenta previa and PPROM have been ruled out.
4. Transvaginal ultrasound (TVS) examination:
    a. Measurement of cervical length:[29]
        i. A short cervix of <3 cm before 34 weeks has an increased risk of preterm birth.
5. Obstetrical ultrasound examination:
    a. Assessment of;
        i. Fetus: anomalies, presentation, size, weight;
        ii. Placenta: position, abnormalities;
        iii. Amniotic fluid: volume;

iv. Maternal: anatomic anomalies;
v. Dopplers: in the case of fetal growth restriction.

6. Laboratory evaluation:
   a. Rectovaginal group B streptococcal culture;
   b. Culture for chlamydia/gonorrhea;
   c. Urine culture to diagnose asymptomatic bacteriuria;
   d. fFN in women <34 weeks, cervical dilation <3 cm and cervical length between 2 and 3 cm on TVS:
      i. Measurement of fFN is performed to distinguish women in true preterm labor from those with false labor so as to avoid unnecessary intervention for the 50% of patients that will ultimately have a term birth without tocolysis.[30]
      ii. Qualitative result is positive or negative: A positive fFN test refers to a fFN concentration ≥50 ng/mL in cervicovaginal fluid between 22+0 and 34+6 weeks' gestation in women with intact membranes, cervical dilation <3 cm, and no gross vaginal bleeding. A positive fFN result correlates with an increased risk of preterm delivery within 7 days.[31]
      iii. Quantitative result: uses a 50 ng/mL threshold. A threshold of 10, 50, 200, and 500 ng/mL predict preterm birth within 14 days by 11, 20, 37, and 46%, respectively.[32]
      iv. If fFN testing is negative (concentration 50 ng/ml or less), it is unlikely to be preterm labor.

DIAGNOSIS

Specific criteria used for diagnosis of preterm labor:[33]

Uterine contractions: ≥4 every 20 minutes or ≥8 in 60 minutes

plus

Cervical dilation ≥3 cm **or**

Cervical length <20 mm on transvaginal ultrasound **or**

Cervical length 20–<30 mm on transvaginal ultrasound and positive fetal fibronectin.

TREATMENT

1. ≥34 weeks' gestation:
   a. Admit for delivery after observation for 6 hours if progressive cervical dilation and effacement are documented.
2. <34 weeks' gestation
   a. Maternal antenatal transfer: Women who are at risk of preterm delivery especially prior to 32 weeks should be assessed to be transferred to a unit where there is an NICU to ensure care for the preterm infant.
   b. Administer antenatal corticosteroids to reduce neonatal morbidity and mortality due to respiratory distress syndrome, intraventricular hemorrhage, and other causes.
   c. Administer antibiotics for GBS chemoprophylaxis, because preterm infants have a greater risk of neonatal GBS infection than those born at term, intrapartum prophylaxis with penicillin is recommended.
   d. Administer tocolytic drugs for up to 48 hours to delay delivery, so that antenatal steroids given to the mother can achieve its maximum fetal effect.
   e. Administer magnesium sulfate for pregnancies at 24–32 weeks' gestation. In utero exposure to magnesium sulfate provides neuroprotection against cerebral palsy and other types of severe motor dysfunction in offspring born preterm.

Antenatal corticosteroids

1. Evidence has shown that a single dose course of antenatal corticosteroid therapy administered to women at risk for preterm birth reduces the risk of respiratory distress syndrome, intraventricular hemorrhage and necrotizing

enterocolitis.[34]

2. Gestational age at administration:
   a. **22+0 to 33+6 weeks**: if delivery in the next 1–7 days is anticipated with planned neonatal care. Evidence has shown that the risk of major morbidity is still high even with the administration of the antenatal steroids
      i. If not delivered, a single repeat course of antenatal corticosteroids may be needed later in gestation when the treatment is thought to be more effective.
   b. **>34+0 weeks:** use of antenatal steroids is controversial because of the inconsistent data available; however, clinical approaches vary and some clinicians will still administer corticosteroids prior to delivery due to the reduction in neonatal respiratory morbidity especially if the mode of delivery is by cesarean section as respiratory problems are less common after labor and vaginal birth.
      i. **34+0 to 36+6 weeks**: The American College of Obstetricians and Gynecologists (ACOG) recommends the administration of antenatal corticosteroids for women with singleton pregnancy at risk of imminent preterm birth within 7 days.[35]

Antibiotics for GBS chemoprophylaxis

1. Women with a known positive GBS culture within the previous 5 weeks should be given GBS prophylaxis if admitted in preterm labor.
2. If colonization status is unknown, GBS cultures are obtained at the time of presentation and then antibiotic prophylaxis is administered
3. GBS prophylaxis is continued until delivery if true preterm labor; however, if after a period of observation and the patient is not in true labor then the antibiotics should be discontinued.
4. If the culture result is negative, no GBS prophylaxis is needed if preterm labor recurs within the next 5 weeks.
5. If the patient is undelivered at 36+0 to 37+6 weeks' gestation, a vaginal–rectal culture should be repeated

Tocolysis

1. Administration of tocolytic drugs (Table 2) can reduce the strength and frequency of uterine contractions.
2. Evidence has shown that tocolytic drugs are more effective than placebo/control for delaying delivery for a maximum of 48 hours to 7 days. Tocolysis therapy should not be used continuously until term gestation is reached.[30]
3. The goal of tocolysis is to delay delivery by at least 48 hours, so that corticosteroids have time to achieve their maximal effects, transfer the mother to a facility where there is appropriate neonatal care or to prolong the pregnancy in the case where conditions that cause labor are treated and are unlikely to cause recurrent preterm labor, e.g. pyelonephritis.
4. Give tocolysis to women:
   a. In early phase of preterm labor, where cervical dilation is still <3 cm;
   b. Gestational age of ≥24[36]–34 weeks' gestation.
5. Contraindications to tocolysis include:
   a. Intrauterine fetal demise;
   b. Lethal fetal anomaly;
   c. Non-reassuring fetal status;
   d. Pre-eclampsia with severe features or eclampsia;
   e. Maternal hemorrhage with hemodynamic instability;
   f. Intraamniotic infection;
   g. Preterm prelabor rupture of membranes;
   h. Medical contraindications to the tocolytic drug.

Table 2 Types of tocolytic drugs.

Drug	Mode of action	Efficacy	Maternal side-effects	Fetal side-effects	Contraindications
Cyclooxygenase	Cyclooxygenase	Reduces the	Nausea,	In utero closure	Platelet

Drug	Mode of action	Efficacy	Maternal side-effects	Fetal side-effects	Contraindications
inhibitors, e.g. indomethacin	is the enzyme responsible for conversion of arachidonic acid to prostaglandins, which are critical in parturition, thus cyclooxygenase inhibitors reduce prostaglandin production	risk of delivery within 48 hours of initiation compared to any beta-agonist, but as effective as nifedipine	esophageal reflux, gastritis, and emesis: platelet dysfunction (rare)	of ductus arteriosus (risk associated with use for >48h) and oligohydramnios. PDA in neonate	dysfunction or bleeding disorder, hepatic or renal dysfunction, gastrointestinal or ulcerative disease, asthma (in women with hypersensitivity to aspirin)
Calcium channel blockers, e.g. nifedipine	Directly block the influx of calcium ions through the cell membrane and inhibit release of intracellular calcium from the sarcoplasmic reticulum and increase calcium efflux from the cell. The resulting decrease in intracellular free calcium inhibits calcium-dependent myosin light-chain kinase phosphorylation, leading to myometrial relaxation	Reduces the risk of delivery within 48 hours. Benefits over beta-agonists with respect to prolongation of pregnancy, neonatal morbidities and maternal adverse effect	Dizziness, flushing, headache, palpitations, elevation of hepatic aminotransferase levels		Hypotension, preload-dependent cardiac lesions (e.g. aortic insufficiency)
Beta-agonists, e.g. ritodrine and terbutaline	The beta-2 receptor agonists cause myometrial relaxation by binding with beta-2 adrenergic receptors and increasing intracellular adenyl cyclase	Decreases the number of women giving birth within 48 h	Tachycardia and hypotension, tremor, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, hyperglycemia	Tachycardia	Tachycardia-sensitive maternal cardiac disease, poorly controlled diabetes mellitus
Oxytocin-receptor antagonists, e.g. atosiban	Selective oxytocin-vasopressin receptor antagonist	Use of these drugs does not reduce the risk of birth within 48 hours of	Hypersensitivity injection-site reactions	For atosiban, an increased rate of fetal or infant death (may be attributable to the lower	None

Drug	Mode of action	Efficacy	Maternal side-effects	Fetal side-effects	Contraindications
		initiation of treatment, the risk of preterm birth at less than 28 weeks' gestation or the risk of preterm birth at <37 weeks		gestational age of infants in the atosiban group)	
Nitric oxide donors, e.g. glyceryl trinitrate	Nitric oxide is produced in a variety of cells and is essential for maintenance of normal smooth muscle tone. Extracellular stimuli of NO formation to the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP). The increase in cGMP content in smooth muscle cells activates myosin light chain kinases leading to smooth muscle relaxation	Use of glyceryl trinitrate does **not** significantly prolong pregnancy by ≥48 h, reduce preterm birth, or result in improved neonatal outcomes compared to placebo, beta agonists and nifedipine	Dizziness, flushing, hypotension		Hypotension, preload-dependent cardiac lesions (e.g., aortic insufficiency)
Magnesium sulfate	Competes with calcium at the level of the plasma membrane voltage-gated channels and inhibits myosin light-chain kinase activity, reducing myometrial contractility	Administration does **not** result in a statistical reduction in birth <48 h. Neither more nor less effective than other tocolytics	Flushing, diaphoresis, nausea, loss of deep-tendon reflexes (serum levels of 9.6–12mg/dL), respiratory paralysis (at serum levels of 12–18mg/dL), cardiac arrest (at serum levels of 24–30mg/dL); when used with calcium channel blockers, suppression of heart rate, contractility, and left ventricular systolic pressure and		Myasthenia gravis

Drug	Mode of action	Efficacy	Maternal side-effects	Fetal side-effects	Contraindications
			neuromuscular blockade		

1. Clinical practice dictates which tocolytic is used.
   a. 24–32 weeks: indomethacin has been suggested as first-line therapy for labor inhibition due to its reduced side-effect profile and its compatibility with magnesium sulfate which is used concomitantly for neuroprotection.
   b. 32–34 weeks: nifedipine is used as first-line therapy, followed by terbutaline as second-line therapy.

Magnesium sulfate for neuroprotection

Multiple large studies have shown that antenatal administration of magnesium sulfate has been associated with a reduction in cerebellar hemorrhage in preterm infants[37] with a reduction in cerebral palsy.[38,39,40,41] The mechanism of action is poorly understood; however, several have been proposed including stabilization of the cerebral circulation and protection against oxidative, inflammatory and excitatory injury.

Candidates:

1. Women at high risk of imminent (within 24 hours) preterm birth
2. >24–<32 weeks' gestation

Administer for 24 hours (even if delivery has not occurred), repeat doses are not advised.

Prevention of preterm birth

When a woman presents acutely in established preterm labor, efforts to delay delivery are somewhat unsuccessful. A lot of research has therefore been performed in prevention strategies.

Progesterone supplementation

Physiologically, progesterone helps maintain pregnancy in many ways; its production from the corpus luteum is critical in early pregnancy until the placenta takes over, it helps maintain uterine quiescence and prevents apoptosis in the fetal membranes in pro-inflammatory conditions.

The efficacy of progesterone supplementation depends on appropriate patient selection which is summarized in Table 3.

Pregnancies likely to benefit include:

1. Women with a singleton pregnancy who have had a previous spontaneous preterm singleton birth.
   a. A meta-analysis in 2013 showed that in women with a past history of preterm birth, progesterone supplementation resulted in a lower risk of subsequent preterm birth and a lower risk of neonatal morbidity including use of assisted ventilation, incidence of necrotizing enterocolitis and NICU admission.[42]
   b. The use of hydroxyprogesterone caproate injection is supported by a randomized controlled trial by Meis *et al.*, where active prophylaxis with progesterone injections reduced the risk of preterm delivery at all gestational ages studied.[43] However, the PROLONG trial reported no significant reduction in preterm birth or neonatal morbidity when women were supplemented with hydroxyprogesterone caproate injection.[44]
   c. There have been conflicting studies regarding the use of vaginal progesterone pessaries. A Brazilian trial showed that daily supplementation with vaginal progesterone gel from 24 to 34 weeks' gestation significantly reduced the risk of preterm delivery.[45] Again, two studies the OPPTIMUM and PROGRESS studies both subsequently showed that supplementation with vaginal progesterone did not reduce fetal death/birth before 34 weeks, neonatal respiratory distress syndrome and other morbidities.[46,47]
2. Women with a short cervix on ultrasound examination in the current pregnancy.
   a. A recent systematic review has found that supplemental vaginal progesterone in women with a short cervix of <25 mm before 24 weeks reduces the risk of preterm birth, neonatal morbidity including respiratory distress, reduced birth weight and reduced admission to NICU.[48]

Table 3 Patient selection for progesterone supplementation. Adapted from Committee on Practice Bulletins-Obstetrics TACoO, Gynecologists.[49]

Indication	Progesterone supplementation indicated	Management
Singleton pregnancy, prior spontaneous singleton preterm birth, normal cervical length	Yes	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks' gestation and continuing through 36 weeks' gestation or until delivery and monitor cervical length. Natural progesterone administered vaginally is a reasonable alternative. Short (≤25 mm) cervix → consider performing cerclage
Singleton pregnancy, prior spontaneous twin preterm birth, normal cervical length	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks' gestation and continuing through 36 weeks' gestation or until delivery and monitor cervical length. Natural progesterone administered vaginally is a reasonable alternative. Short (≤25 mm) cervix → consider performing cerclage
Singleton pregnancy, no prior spontaneous preterm birth, short cervix (≤20 mm)	Yes	Progesterone suppository 90–200 mg vaginally each night from time of diagnosis through 36 weeks' gestation. A vaginal suppository can be prepared by a compounding pharmacy utilizing a commercially available standardized kit. Other options include a 100 mg micronized progesterone vaginal tablet or an 8% vaginal gel containing 90 mg micronized progesterone per dose. Both preparations are commercially available in US, but not approved for prevention of preterm birth in cervical shortening
Multiple pregnancy (twins or triplets) without prior preterm birth, normal cervical length	No	No progesterone, no cerclage
Twins, prior preterm birth	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 week' gestation and continuing through 36 weeks' gestation or until delivery. Natural progesterone administered vaginally is a reasonable alternative.
Twins, short cervix	Possibly	Vaginal progesterone, no cerclage
Preterm premature rupture of membranes	No	–
Positive fetal fibronectin test	No	–
Undelivered after an episode of preterm labor	No	–

Evaluation of cervical length

Cervical shortening is one of the first steps leading to labor. This process usually begins at the level of the internal os and progresses downwards towards the external os, therefore it is often detected on ultrasound rather than on physical examination.[50] Most women do not have a short cervix and of those who do, only 30% will deliver prior to 35 weeks;[51] however, cervical length screening can still be cost-effective.

The diagnosis of a short cervix is when cervical length is ≤25 mm before 24 weeks' gestation. The threshold that triggers treatment varies worldwide. The diagnosis of a short cervix is when cervical length is ≤25 mm before 24 weeks' gestation. The threshold that triggers treatment varies worldwide for example The American College of Obstetricians and Gynecologists (ACOG) use a cervical length of ≤20 mm in women with no prior spontaneous birth and <25 mm in women with a prior spontaneous preterm birth at <34 weeks' gestation in order to initiate treatment.[49]

Treatments triggered include:

1. Vaginal progesterone: in singleton pregnancies without a prior spontaneous preterm birth;
2. Cervical cerclage (ultrasound indicated): in singleton pregnancies with a prior spontaneous preterm birth.

Universal screening of cervical length is supported by one study which showed that up to 40% of women with a short cervix are missed when selective cervical screening is performed[52] and screening women without a history of preterm birth reduces the frequency of spontaneous preterm birth at <37, <34 and <32 weeks' gestation. A 2019 meta-analysis of randomized trials did not find sufficient evidence to recommend routine cervical length screening for all pregnant women;[53] however, there is a consensus for screening high-risk women with singleton pregnancies.

Screening with transvaginal ultrasound

1. Women with no prior spontaneous preterm birth are screened once at approximately 20 weeks ' gestation (18–24 weeks);
2. Women with a prior spontaneous preterm birth usually begin screening at approximately 16 weeks' gestation and the frequency depends on the measurement.

PRACTICE RECOMMENDATIONS

- **Identification of the many risk factors that can contribute to preterm labor is essential before conception or early in pregnancy to allow for interventions.**
- **A history of prior preterm birth is the strongest risk factor for future preterm birth.**
- **Diagnosis of preterm labor is based on specific clinical criteria that includes both regular painful contractions of the uterus and cervical dilation and/or effacement.**
- **Women >34 weeks' gestation in preterm labor are admitted for delivery as perinatal morbidity and mortality are low compared to the potential complications and costs that can result from labor inhibition at this gestation.**
- **For women diagnosed in preterm labor, consider maternal transfer to a facility with a NICU, administer tocolytic drugs for 48 hours, antibiotics for group B streptococcal chemoprophylaxis, antenatal corticosteroids and magnesium sulfate for neuroprotection (between 24 and 32 weeks' gestation)**
- **Tocolysis:**
  - **24–32 weeks: indomethacin as first-line therapy and nifedipine as second-line therapy;**
  - **32–34 weeks: nifedipine as first-line therapy and terbutaline as second-line therapy.**
- **Prevention:**
  - **Progesterone supplementation in a woman with a history of preterm birth reduces the risk of recurrent preterm birth by 30%'**
  - **Screening with transvaginal ultrasound:**
    - **Women with no prior spontaneous preterm birth are screened once at approximately 20 weeks' gestation (18–24 weeks).**

- **Women with a prior spontaneous preterm birth usually begin screening at approximately 16 weeks' gestation and the frequency depends on the measurement.**
    i. **For women with no previous history of preterm delivery who develop a short cervix, progesterone supplementation may prolong gestation.**
    ii. **For women with a history of preterm delivery, who develop a short cervix despite progesterone supplementation, placement of a cerclage may prolong gestation.**

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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