Preterm birth

- challenges and opportunities
  in prediction and prevention

PerkinElmer
For the Better
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What is preterm birth?

Definition

A full-term human pregnancy lasts 40 weeks. Delivery that occurs before 37 completed weeks of pregnancy is considered to be preterm birth, regardless of birth weight (World Health Organization). Although all births before 37 weeks of gestation are defined as preterm, most damage and death occurs in infants delivered before 34 weeks [1, 2]. It is therefore often convenient to consider preterm birth as being divided into subgroups such as extremely preterm, very preterm, moderately preterm and, sometimes, late preterm.

- Preterm, birth occurring from 23 to 37 weeks
- Late preterm, birth at 34-36 weeks
- Moderately preterm, birth at 32-34 weeks
- Very preterm, before 32 weeks
- Extremely preterm, before 28 weeks

Preterm birth can be either spontaneous or iatrogenic (induced by the physician). About 20% of all preterm deliveries are iatrogenic. In these the physician has decided that the baby needs to be delivered preterm, due to serious maternal or fetal complications such as severe pre-eclampsia (PE) or intra uterine growth retardation (IUGR). In these cases labor is medically induced or a cesarean section is performed.

Spontaneous preterm birth

Classically categorized, spontaneous preterm birth is associated with either preterm labor (PTL) or preterm premature rupture of fetal membranes (PPROM) [3,4] (Figure 1). Preterm labor is defined as labor (regular contractions and cervical ripening) starting before 37 complete weeks of gestation, with or without intact fetal membranes. PPROM is defined as rupture of fetal membranes prior to 37 weeks gestation and it very often leads to preterm birth. Spontaneous preterm birth is a common and serious public health problem. In the remainder of this booklet, unless distinction is made, preterm birth or PTB should be understood to mean spontaneous preterm birth.
Low birth weight

A low birth weight (LBW) baby is one that weighs less than 2,500 grams at delivery, regardless of the gestational age at birth. This means that low birth weight babies are not necessarily born prematurely, although there is an obvious association between birth weight and prematurity (Figure 2). In developed countries, most low-birth weight infants are preterm. In under-developed countries, the proportion of term low-birth weight infants is higher due to the greater prevalence of malnutrition. The low birth weights may also be divided into the additional categories, very low birth weight (VLBW), and extremely low birth weight (ELBW).

- Low birth weight, less than 2500 g
- Very low birth weight, less than 1500 g
- Extremely low birth weight, less than 1000 g

Low birth weight babies include both those born preterm and those whose growth has been impaired in utero. A baby whose weight is significantly lower than the population norm is termed small for gestational age, SGA. The cut-off level is usually weight below the 10th percentile for gestational age. An SGA baby is thus smaller than 90 percent of all other babies of the same gestational age. SGA has been defined in some publications on the basis of length rather than weight. Alternative cut-off levels such as the 5th, or 3rd percentile for gestational age have also been applied.

The cause of SGA can be either pathological or non-pathological. Intrauterine growth restriction, IUGR is a failure of normal fetal growth. It is caused by multiple adverse effects on the fetus that prevent normal growth potential from being realized. IUGR and SGA are related terms but are not synonymous. Not all IUGR infants are small enough to meet the criteria for SGA and not all SGA infants are small as a result of a growth restrictive process for which the term IUGR would be appropriate.

Figure 2. An overlap between preterm birth and low birth weight.
**Preterm birth rate**

Premature birth occurs in one in ten pregnancies. There are about 13 million PTBs annually worldwide. The incidence is about 11% in North America, about 5.6% in Oceania and about 5.8% in Europe (Table 1) [5]. In the US, on average, one preterm baby is born every minute. Since 1990, for reasons that are not fully understood, worldwide the preterm birth rate has risen by approximately 14%. The increase over the past decade may in part be explained by increasing iatrogenic preterm births, increasingly aggressive resuscitation of very preterm babies, higher maternal age, higher rates of assisted reproductive technologies (ART) and multiple gestations related to these technologies. Singleton pregnancies after in-vitro fertilization are also at increased risk of preterm birth [190]. This increase is quite alarming, considering that preterm birth is associated with a significant risk of disease and death in the newborn baby. Rates of preterm delivery are not distributed evenly among fertile women. It has been observed that the prevalence of PTB is twice as high in African-American women compared with Caucasians or Hispanic women in the US. Preterm birth rates are in the range of 16-18 % among black women compared with 5-9 % for white women in the US and UK. Black women are also three to four times more likely to have a very early preterm birth than women from other racial or ethnic groups [193]. Also the causes of preterm births differ by ethnic group. Preterm birth is most commonly caused by preterm labor in white women, while PPROM is the more frequent cause in black women [189].

Table 1. Assessments of preterm birth rates in various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Preterm birth rate</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>12.7 %</td>
<td>[6]</td>
</tr>
<tr>
<td>Canada</td>
<td>7.6 %</td>
<td>[7]</td>
</tr>
<tr>
<td>UK</td>
<td>7.6 %</td>
<td>[8]</td>
</tr>
<tr>
<td>Germany</td>
<td>7.6 %</td>
<td>[9]</td>
</tr>
<tr>
<td>France</td>
<td>6.2 %</td>
<td>[9]</td>
</tr>
<tr>
<td>Finland</td>
<td>5.2 %</td>
<td>[10]</td>
</tr>
<tr>
<td>Sweden</td>
<td>5.6 %</td>
<td>[11]</td>
</tr>
<tr>
<td>Norway</td>
<td>8.5 %</td>
<td>[12]</td>
</tr>
<tr>
<td>Denmark</td>
<td>6.1 %</td>
<td>[207]</td>
</tr>
<tr>
<td>Australia</td>
<td>7.9 %</td>
<td>[206]</td>
</tr>
<tr>
<td>Mozambique</td>
<td>15.4 %</td>
<td>[13]</td>
</tr>
</tbody>
</table>
Why the concern?

Preterm birth is a serious health problem. It is associated with a significant risk of disease and death of the newborn baby. Preterm birth surpassed birth defects as the leading cause of neonatal death in 2001 [14]. Improvements in neonatal care have led to higher survival of very premature infants but premature babies are still at great risk for adverse health and developmental problems compared with term infants. The risks are highest at the lowest gestational ages. (Figure 3). According to a recent study infant survival was significantly lower when the onset of preterm birth was PPROM as compared with preterm labor and iatrogenic delivery [87].

![Figure 3](image)

Figure 3. Numbers of live and healthy babies by gestational age. Data points from [19, 20].

The emotional impact on a family encountering this problem is enormous. In many cases the baby is admitted to a hospital far from the family home, and parents and siblings suffer considerable anxiety, with doubts about the baby’s survival and full recovery.

Premature babies are at increased risk for both newborn health complications and for lasting disabilities, such as mental retardation, cerebral palsy (CP), lung and gastrointestinal problems and vision and hearing loss (Table 2). Babies born just a few weeks early are also six times more likely to die in their first week of life than full-term babies and three times more likely to die before their first birthday [15]. In the long term, children born prematurely have an increased
risk of cardiovascular disease, hypertension and diabetes as adults and a possible increase in cancer risk [16, 17]. Prematurity-associated medical complications also portend future educational and occupational impairment that extend into late childhood and beyond. In a Swedish study preterm birth was found to be associated with a lower chance of completing a university education and a lower net salary [18].

Table 2. Complications and disabilities related to prematurity [18].

<table>
<thead>
<tr>
<th>Neonatal</th>
<th>Short term</th>
<th>Long term</th>
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</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome (RDS)</td>
<td>Feeding and growth difficulties</td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (IVH)</td>
<td>Infection</td>
<td>Sensory deficits</td>
</tr>
<tr>
<td>Periventricular leukomalacia (PVL)</td>
<td>Apnea</td>
<td>Special health care needs</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (NEC)</td>
<td>Neurodevelopmental difficulties</td>
<td>Incomplete catch-up growth</td>
</tr>
<tr>
<td>Patent ductus arteriosus (PDA)</td>
<td>Retinopathy</td>
<td>Difficulties at school</td>
</tr>
<tr>
<td>Infection</td>
<td>Transient dystonia</td>
<td>Behavioral problems</td>
</tr>
<tr>
<td>Metabolic abnormalities</td>
<td></td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td></td>
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</tr>
</tbody>
</table>

Cost of the disorder

Preterm birth is associated with substantial use of healthcare resources. The economic cost of preterm birth is not well established but the emerging data are alarming. The costs of a preterm birth are not just those incurred while in the hospital’s neonatal intensive care unit. Some health problems that develop at this time can persist for years. It was recently estimated that preterm/low birth weight infants in the United States account for half of infant hospitalization costs and one quarter of pediatric costs, suggesting that major infant and pediatric cost savings could be realized by preventing preterm birth [22].

Studies in the United Kingdom and Ireland show that the cumulative costs of hospital admissions incurred during the first 10 years of life are more than twice as high in preterm infants compared to children born at term [208].
It has been predicted that even higher cost differences will occur at a later age, especially in the extremely preterm group. The increasingly complex educational and job demands in society are exacerbating the lifelong problems associated with preterm birth [209]. A study in Norway has shown that very early preterm birth is associated with a significantly increased risk in mortality during childhood especially in males, decreased reproductive performance in later life for both sexes, and increased risk of having preterm offspring in preterm women [210].

Compared with term births premature births are associated with significant incremental expenditures.

- Maternal delivery costs
- Early intervention costs
- Special education costs
- Rehabilitation for physical handicaps
- Lifelong care
- Family support
- Lost household productivity costs related to cerebral palsy, mental retardation and hearing impairment.

Predictably, the costs associated with preterm infants are gestational age dependent. The highest costs per case generally occur in the very preterm and extremely preterm groups but the incremental aggregate annual medical care cost for the large number of infants born between 28 and 32 weeks is approximately 80% of the aggregate cost for infants born at less than 28 weeks. The loss of human potential cannot be calculated.

**Public knowledge about preterm birth**

A study conducted in 2002 in the US revealed that there is considerable misunderstanding of preterm birth among adults. Although nearly one in eight babies is born prematurely, most U.S. adults do not consider prematurity to be a serious public health problem. While the etiology can be identified in only half of spontaneous preterm births, the public largely blames the mother's prenatal behavior. Misperceptions are prevalent and may impede future research and prevention efforts if not corrected. [23] The general public, and health professionals, need to be aware that it is still not known what initiates the spontaneous onset of labor in women and this makes the prevention and management of preterm labor difficult. There is a need for more clinical and laboratory research into preterm labor and public pressure can be instrumental in persuading governments and research foundations to put more resources into this area. [211]
**Symptoms**

The symptoms of preterm labor include:

- Uterine contractions every 10 minutes or more often
- Change in vaginal discharge (leaking fluid or bleeding from vagina)
- Pelvic pressure
- Low, dull backache
- Cramps that feel like period pains

**Risk factors**

Preterm labor and delivery can occur in any pregnancy, but some women are more prone than others. Several demographic characteristics associated with an increase risk of preterm birth have been identified.

- **Previous preterm birth.**
  This is the strongest risk factor for spontaneous preterm labor. Women with a history of preterm birth have a significantly increased risk of subsequent preterm birth.
- **Multifetal pregnancy (twins, triplets or more)**
- **Low socioeconomic status**
- **African-American ancestry**
  (although it may be difficult to separate ethnicity from socioeconomic factors)
- **Extremes of weight (underweight or obesity)**
- **Extremes of age <16 or >35**
- **Tobacco use**
- **Stress**
- **Genital tract infection**
- **Preterm premature rupture of the membranes (PPROM)**
- **Antepartum hemorrhage**
- **Cervical incompetence**
- **Congenital uterine abnormalities**

The mechanisms by which the maternal demographic characteristics are related to preterm birth are unknown. Risk factors for PPROM are generally similar to those for preterm labor with intact membranes although infections and tobacco exposure play important roles [191]. The most common reasons for iatrogenic preterm deliveries are pre-eclampsia and other medical disorders in pregnancy, intrauterine fetal growth restriction, congenital abnormalities and trauma [212].
Etiology

The etiology of preterm birth, like the mechanism of term labor, is unclear. It is though to be a multifactorial, complex disorder with both physiopathological, genetic and environmental factors. The “preterm labor syndrome” proposes that preterm labor is the result of multiple causes including infection/inflammation, uterine stretch and vascular disorders [213]. However, it is not known whether preterm labor results from a physiological process similar to term labor, but occurring too early in pregnancy, or whether it is a pathological process resulting from an abnormal set of signals.

Infection and inflammation

Infections seem to be associated with some preterm births. It has been suggested that bacterial infection that spreads to the uterus and amniotic fluid may trigger inflammation and consequently preterm labor or preterm rupture of membranes. Goldenberg et al. reported that up to 80% of women who deliver before 30 weeks of gestation have evidence of bacterial infection of the amniotic fluid and/or membranes, compared with only 30 % of those who deliver after 37 weeks of gestation.[24]

Maternal urogenital infections

Vaginal infections such as bacterial vaginosis (BV) are thought to be related to preterm birth. As the most common lower genital tract infection in women of reproductive age, BV is a mainly asymptomatic syndrome in which the normal vaginal lactobacilli are replaced by a mixed flora with high concentrations of anaerobic bacteria Gardnerella vaginalis and Mycoplasma homnis. BV may result in a vaginal discharge, which can be grey in color and with characteristic “fishy” odor. Its presence in pregnancy is associated with a two-fold increase in the risk of preterm birth. Other forms of infection connected to preterm birth include urinary tract infections that progress to pyelonephritis (kidney infection) [25], asymptomatic bacteriuria (presence of bacteria in urine) [26,27] and some sexually transmitted diseases such as chlamydia [28]. Andrews et al. 2000 found that women with chlamydia had up to three times the risk of PTB [28]. Presence of the bacteria Ureaplasma urealyticum, Fusobacterium spp. [29], Trichomonas vaginalis, Klebsiella pneumoniae, Escherichia coli and Hemophilus vaginalis have also been associated with PTB. The role of group B. streptococcus is unclear [30].
Viral infections may be associated with PTB. Spontaneous second trimester loss was demonstrated to be strongly associated with any viral infection in placental tissue [231]. According to a recent study, human papillomavirus (HPV) infection of extravillous trophoblast induces cell death and may reduce placental invasion into the uterine wall. Thus, HPV infection may cause placental dysfunction and is associated with adverse pregnancy outcomes, including spontaneous preterm delivery [233]. Also exposure to Cytomegalovirus (CMV) may be associated with PTB [232].

Chorioamnionitis (infection of fetal membranes and amniotic fluid) is strongly associated with preterm birth. The earlier the preterm birth the stronger the association [24, 31, 32]. Inflammatory infiltration of the fetal membranes and decidua in early preterm labor provokes a large increase in prostaglandin output by these tissues, which may trigger delivery [214]. An underlying mechanism is apparently an ascending bacterial infection from the lower genital tract to the chorio-decidual space and subsequently to the amniotic cavity and fetus (Figure 4). Some investigators believe that normal delivery is associated with a local inflammatory process leading to the liberation of uterotonic agents. In the course of an ascending infection, the inflammatory cascade may be prematurely activated [33]. Since the membranes generally form a barrier to ascending infection, a common complication of PPROM is development of intrauterine infection and preterm labor [192]. Microorganisms produce enzymes such as proteases and mucinases, which allow penetration of the cervical mucous plug favoring the ascent of bacteria [34]. Bacteria also release phospholipases, which initiate the formation of arachidonic acid, from which prostaglandins are produced. Prostaglandins are important mediators of uterine activity. They have a pivotal role in contraction of the smooth muscle of the uterus and the biophysical changes associated with cervical ripening. Bacteria also release endotoxins, which cause release of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-1 (IL-6) and tumor necrosis factor (TNF). The proinflammatory cytokines in turn stimulate the expression of enzymes in the prostaglandin biosynthetic pathway [35]. Microorganisms also enhance the production of matrix metalloproteinases, leading to the breakdown of the fetal membranes, ripening of the cervix and uterine contractions [36].

The remaining question is why do some women with colonized genitourinary tract bacteria deliver preterm while others do not? The possible explanation is that individual variations in inflammatory response may contribute to the occurrence of preterm birth. According to studies, inflammatory activation occurs only moderately with term labor, but much more robustly in preterm delivery,
particularly in the presence of intrauterine infection. [33] The importance of the cervix as a barrier to ascending infection is also suggested by the increased frequency of chorionamnionitis in premature cervical dilation with or without cerclage. The cervical mucus plug, which thickens following conception, may have an important role as a local immunological gatekeeper. This is supported by the fact that most pregnancies continue to term despite the presence of potentially pathogenic microbes in the vagina. The cervical mucus is also a rich source of antimicrobial proteins and peptides, including lysozyme, lactoferrin, defensin and immunoglobulins so the mucus plug is not only a mechanical but also a chemical barrier to infection that ascends from the vagina [152].

Figure 4. Ascending bacterial infection. Modified from [24, 29].
Infections at other sites

Infection, even remote from the uterus, may activate an inflammatory process that triggers a uteroplacental response leading to preterm delivery. Systemic infections associated with preterm delivery include appendicitis (inflammation of the appendix usually due to a blockage inside it), pneumonia (inflammation of the lungs), and periodontal disease (gum inflammation). In a systemic infection microorganisms invade the bloodstream and spread via circulating blood to several organs.

In recent years there has been a mounting body of evidence that indicates an association between periodontal disease and preterm birth. Periodontal disease or periodontitis, is a Gram-negative, anaerobic infection of the oral cavity which results in degradation of the bones and connective tissue which support the teeth. The destruction of these supporting structures involves both direct tissue damage caused by bacterial products and indirect damage caused by the cytokines that appear in the gingival fluid as part of the host immune response [37]. While periodontal disease affects up to 50% of the population, there is a relatively high incidence of periodontal disease among pregnant women [38, 39]. Periodontal disease has also been shown to be associated with delivery of SGA infants [40]

Maternal-fetal conflict and infection

To establish and maintain a pregnancy, the immune response, which normally destroys foreign material, must make an exception for the fetus. 50% of the fetal genes are inherited from the father and as a result the fetus produces paternal antigens that should be targeted for destruction by the maternal immune system [41]. In the presence of infection maternal immune pressure may favor fetal expulsion if overall maternal reproductive interests outweigh fetal interests. Both mothers and babies exposed to amniotic fluid infection are at risk of sepsis (an infection of the blood) and, eventually, death. Intrauterine infection may also elicit a fetal inflammatory response [42, 43, 44]. The fetal inflammatory response syndrome (FIRS) is a condition characterized by systemic inflammation of the fetus and an elevation of fetal plasma IL-6. FIRS is associated with the impending onset of preterm birth. Babies who survive the inflammatory-mediated insult of preterm delivery are at higher risk of critical illness including cerebral palsy. There is thus evidence to support the idea that the preterm onset of labor may be the fetus’ mechanism to exit a hostile intrauterine environment. [45, 46]
Inflammation without infection

Inflammatory response can occur also in the absence of microbial infection, and is thus also called sterile inflammatory response. Inflammatory response in the membranes appears to be associated with normal parturition. A sterile inflammatory response has also been shown to be sufficient to cause PPROM and preterm labor [167]. Both infection driven and sterile inflammation induce many of the same cytokine receptors but they probably have distinct pathways. There are many different stimuli capable of causing sterile inflammation. Relaxin expression is one of them. Relaxin is a collagenolytic hormone that causes increased production of the matrix metalloproteinases. Relaxin causes increased secretion of cytokines IL-6 and IL-8 from the membranes, with a similar but less robust effect than infection [168].

Genetic risk factors

It has long been proposed that there is a maternal or fetal genetic predisposition toward PTB. There is a body of evidence to support this argument.

• Women who deliver prematurely are at a greater risk of preterm delivery during their subsequent pregnancies [47, 48].

• There is a tendency for repeat preterm birth to occur at the same gestational age as the previous pregnancies.

• A woman who herself was delivered preterm is more likely to suffer spontaneous preterm labor and preterm birth [49].

• Mothers with an older sister who has given birth to a preterm infant had an 80% higher risk of giving birth to a preterm infant [48].

• It has long been recognized that there is a racial predisposition to preterm birth with African-American mothers being more prone than Hispanic mothers, who are, in turn, more prone than Caucasian mothers.

Genetic differences between individuals i.e. gene polymorphisms, can result in variations in production and activity of proteins. Researchers have begun to investigate the effects of candidate gene polymorphisms on PTB, focusing on polymorphisms related to inflammatory and immune response because of the evidence of involvement of inflammation in pregnancy and parturition. Discovery of a specific gene that predisposes women to PTB would signify an enormous scientific breakthrough that could possibly suggest novel therapeutic and preventive targets.
Maternal genome

One significant candidate gene associated with PTB is the gene coding for tumor necrosis factor alpha (TNF-α), a proinflammatory cytokine present in amniotic fluid of women with intrauterine infection who deliver preterm [50]. Homozygosity of the less common allele, TNF-2 that correlates with enhanced TNF-α production has been associated with PTB in several studies [51, 52, 53]. It has also been documented that black women who were carriers of the IL-6 allele and had bacterial vaginosis had a two fold greater risk of preterm birth than white women [198]. The effect on birth weight of an interaction between maternal smoking and gene polymorphism has also been described [199].

Fetal genome

The fetus also has potential to influence pregnancy outcome. A recent study found an association between multifetal pregnancies and PPROM in cases where the first-born fetus had a TNF-2 genotype. The researchers speculated that the possession of the TNF-2 allele by the fetus nearest the uterine cervix will result in a higher concentration of TNF-α at the membrane surface adjacent to the cervix and promote the rupture of membranes [54].

Paternal genome

The genetic effects of the paternal genome are not clear. There is evidence that changing partner between the first two births increases the risk of infant mortality, preterm birth, and low birth weight for the second birth compared with having the same partner. Increased risk of preterm birth was considered more likely to reflect changes in lifestyle rather than genetic changes or different paternal antigens [56]. Findings from another study suggest that the effect of changing paternity depends on the pregnancy outcome with the previous partner and support the hypothesis that parental human leukocyte antigen (HLA) sharing may be related to preterm delivery [55]. This finding is consistent with our knowledge that inbred mating is associated with deleterious reproductive outcomes. It is now generally recognized that to sustain a pregnancy without rejecting the fetus that carries alloantigens, a mother needs to establish immunologic tolerance. Although still not well understood, the tolerance is probably initiated by fetal (via paternal) immunologic stimulation. Parental HLA sharing results in a lack of adequate antigenic stimulation and failure to establish the maternal immune tolerance, which could lead to a series of adverse pregnancy outcomes [235].
Gene environment interaction

Studies suggest that multiple genetic and environmental factors may affect the risk of PTB independently or interactively. The contribution of genes is still controversial. Although certain gene mutations increase the risk of PTB, there are many women who have these mutations but experience normal delivery. This fact has led some to hypothesize that these mutations require the presence of certain environmental stimuli to have clinical significance. For example, pregnant women or their fetuses who are genetically programmed to produce high levels of pro-inflammatory mediators would be more likely than those producing low levels to exceed the threshold necessary to initiate preterm labor in response to environmental factors. [57] Further research into genetic risk factors in preterm birth is much needed because most of the studies reported so far have been underpowered and are inconclusive.

**Biological pathways leading to preterm birth**

Studies of the epidemiology and pathophysiology of preterm labor have suggested four pathways that may lead to preterm birth.

- **Infection and inflammation**
- **Activation of maternal-fetal hypothalamic-pituitary-adrenal (HPA) axis**
- **Decidual hemorrhage (bleeding)**
- **Uterine stretching**

Risk factors for preterm birth frequently initiate the pathogenic pathways leading to preterm birth. Each of the four different pathways will lead to a common final pathway resulting in uterine contractions, cervical dilation, ruptured membranes and ultimately premature delivery. Several pathways may occur simultaneously in one pregnant woman. The four pathogenic pathways leading to preterm birth each have a unique set of biochemical mediators (Figure 5). A potential fifth pathway is susceptibility to environmental toxins [58].

**Infection and inflammation**

Inflammation, caused by maternal urogenital infection or systemic infection at another site accounts for about 40 percent of preterm births. The mechanism leading to PTB may involve activation of cytokines including interleukin-1β (IL-1β) and TNF-α. Cytokines stimulate synthesis of prostaglandins and also enhance the production of matrix metalloproteinases and IL-8, leading to the breakdown of the fetal membranes and ripening of the cervix.
1. Inflammation
   Infection – 40%
   
   Risk factors:
   • Sexually transmitted infections
   • Bacterial vaginosis
   • Periodontal disease
   • Genitourinary infections
   • Pneumonia

2. Activation of maternal-fetal hypothalamic-pituitary-adrenal (HPA) Axis
   Stress – 30%
   
   Risk factors:
   • Maternal psychological or physical stress
     Domestic violence
     Lack of support
     Trauma
   • Fetal physiological stress
     Compromised uteroplacental blood flow
     Placental pathology

3. Decidual hemorrhage
   Abruption – 20%
   
   Risk factors:
   • Smoking
   • Cocain use
   • Hypertension
   • Maternal trauma
   • IUGR
   • Hereditary coagulopathies

4. Uterine distension
   Stretching – 10%
   
   Risk factors:
   • Multifetal pregnancy
   • Polyhydramanios
   • Structural uterine anomalies

Social - environmental risk factors
Genetic risk factors

IL-1 TNF
CRH Estradiol
Thrombin
Myometrial stretch

COMMON FINAL PATHWAY TO PRETERM BIRTH

Uterotonins, Proteases

Contractions  Cervical change  Rupture of membranes

PTB

Figure 5. Potential pathways and mediators of preterm birth.
Activation of maternal-fetal hypothalamic-pituitary-adrenal axis

Premature activation of the maternal or fetal hypothalamic-pituitary-adrenal (HPA) axis in response to maternal or fetal stress is estimated to account for about 30% of preterm births. Maternal stress can be both physical and psychological. There is an increased prevalence of preterm births among unmarried mothers, mothers with low income and among mothers experiencing major stressful events such as racism or personal violence. Fetal stress may be due to problems in the placental function.

Stress raises the risk of preterm delivery apparently by increasing levels of corticotropin-releasing hormone (CRH). CRH mediates pituitary adrenocorticotropic (ACTH) secretion in both the maternal and fetal pathways, which in turn increases maternal and fetal adrenal cortisol secretion. Increased cortisol levels rapidly increase the amount of circulating CRH. The elevated CRH levels cause prostaglandin production. Prostaglandins cause contractions (act as direct uterotonins), cervical ripening and sensitize the myometrium e.g. to oxytocin’s effects. CRH also enhances placental estrogen production by stimulating the secretion of its precursor from the fetal adrenal gland. Estrogens interact with the myometrium leading to contractions and cervical changes.

Decidual hemorrhage

Decidual hemorrhage, means bleeding in the decidua (the tissue of endometrial origin lining of the uterus, which is in contact with the fetal membranes and the placental plate). It is manifested as vaginal bleeding in only a small number of cases. The profile of women at risk of decidual hemorrhage is quite different from that for both infection- and stress-associated preterm delivery. Those susceptible may well be older, married, and well educated women. The pathway is involved in about 20 percent of preterm births, especially those related to PPROM. The possible reason behind the bleeding is placental abruption (separation of the placenta from the wall of the uterus). The risk factors include maternal cigarette smoking and cocaine use, chronic hypertension and pre-eclampsia, maternal trauma, IUGR, and hereditary coagulopathies (defect in the body’s mechanism for blood clotting). Each of these conditions is associated with damage to the uterine spiral arteries.

The biochemical pathway from decidual bleeding to preterm delivery is closely related to thrombin generation. Thrombin acts to stimulate coagulation and clot formation; however, it also stimulates the production of proteases capable of ripening the cervix and damaging fetal membranes, leading to preterm
premature rupture of the membranes. Thrombin may also exert an indirect uterotonic effect on the myometrium and stimulate contractions.

**Uterine stretching**

Premature delivery may be triggered by mechanical stretching of the myometrium caused by an increase in uterine size that exceeds the ability of the uterus to compensate. The risk factors are multifetal pregnancy (twins, triplets or more) or polyhydramnios (too much amniotic fluid). The mechanism involves the transduction of a signal initiated by the mechanical stretch on the uterus through the cellular structures that in turn activates the production of cytokines and prostaglandins.
Screening

Preterm birth fulfills some of the WHO criteria for screening [59]. It is an important health problem for the individual and community, the screening would probably be economically balanced in relation to possible expenditure on medical care as a whole, and there is evidence that treatment started at an early stage would be of more benefit than treatment started later. As for the criteria still lacking, the natural history of the disease is not yet adequately understood, there is no universally accepted treatment or useful intervention for patients with the disease, and a suitable and acceptable screening test or examination is not yet established.

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<tbody>
<tr>
<td>Risk factor scoring system</td>
<td>Points assigned</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 spontaneous abortion</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 spontaneous abortions</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>vaginal bleeding&gt;10 wk</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>urinary tract infection in pregnancy</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>smoking</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>maternal age &gt;40 y</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;2 spontaneous abortions</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;3 induced abortions</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>maternal age &lt;18y</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>previous preterm delivery</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>cervical suture</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>multiple gestation</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>uterine anomaly</td>
<td></td>
</tr>
<tr>
<td>Papiernik-Berkhauer-Creasy risk scoring system</td>
<td>Social factors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Past medical history</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current pregnancy problems</td>
<td></td>
</tr>
<tr>
<td>CLEOPATRA I score</td>
<td>Cervical length (≤ 2.5 cm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous preterm delivery</td>
<td></td>
</tr>
<tr>
<td>CLEOPATRA II score</td>
<td>Fetal fibronectin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervical length (≤ 2.5 cm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Previous preterm delivery</td>
<td></td>
</tr>
<tr>
<td>Delivery Probability Profile (DPP curves)</td>
<td>Combinations of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervical length (≤ 2.5 cm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior preterm birth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fFN</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Risk scoring systems
The traditional method of screening

The traditional method of screening for PTB is based on obstetric history, symptoms or epidemiological risk factors such as previous preterm birth, maternal age, race and smoking status. Several risk scoring systems (Table 3.) focusing on these risk factors have been developed. The most commonly used scoring system is Creasy’s score [60], which is a modified Papiernik-Berkhauer system [61]. The score systems are developed by either ascribing a numerical value to individual risk factors and by weighting risk factors differently depending on their importance or by statistical methods (regression analysis). These predicting methods are neither sensitive nor specific. Thus most women who deliver preterm are not identified by the risk-scoring system and most women identified as high risk do not deliver preterm. About half of the women who experience preterm birth have no obvious risk factors. Furthermore, because a traditional risk factor score is based largely on previous obstetric history its accuracy is particularly low among women expecting their first child; such women constitute approximately 50 % of those affected by PTB. [62] New markers for the prediction of preterm birth have therefore been explored. The new delivery probability profile system [63, 64] that takes into account sonographic and biochemical markers besides traditional risk factors may have more potential than traditional risk factor scoring.

Screening of symptomatic women

It is important to be able to distinguish between inconsequential abdominal pain or uterine activity, and true premature labor. This enables physicians to prevent unnecessary hospitalization of patients who are not at risk of premature delivery and many unwanted side effects and complications of potentially hazardous tocolytic therapy can be prevented. The central problem is that by the time a woman in spontaneous preterm labor is admitted, there may already be irreversible changes in the uterus, which renders futile any attempts to reverse or inhibit the process. There are both invasive and noninvasive commercial tests available to predict preterm birth. Noninvasive tests use samples that are easily obtained, such as cervicovaginal secretions, serum, plasma, urine or saliva. Such tests present little or no risk to the woman and fetus. Commercially available noninvasive tests measure biochemical markers such as cervicovaginal fetal fibronectin (fFN), phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) or salivary estriol. These tests can be useful in identifying women who will not deliver within the next few days but they are not optimal because of limitations in their positive predictive value (Table 4). Invasive tests, such as the MMP-8 bedside test, require amniotic fluid sampling by inserting a syringe to withdraw the fluid. A syringe is usually inserted through the mother’s abdominal wall and the procedure involves a slight increase in the risk of miscarriage.
Table 4. Ability of selected noninvasive markers to predict PTB in symptomatic women (preferably before 37 weeks, if these data not available, other endpoints have been accepted).

<table>
<thead>
<tr>
<th>Marker Combination</th>
<th>Se</th>
<th>LR+</th>
<th>LR-</th>
<th>FP</th>
<th>PPV</th>
<th>NPV</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of IL-6, -8, CL</td>
<td>30</td>
<td>10</td>
<td>0.7</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>[170]</td>
</tr>
<tr>
<td>CRP</td>
<td>38</td>
<td>6.3</td>
<td>0.7</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>[171]</td>
</tr>
<tr>
<td>CRH</td>
<td>39</td>
<td>3.9</td>
<td>0.7</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>[172]</td>
</tr>
<tr>
<td>phlGFBP-1</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>55</td>
<td>90</td>
<td>-</td>
<td>[173]</td>
</tr>
<tr>
<td>fFN</td>
<td>-</td>
<td>1.83</td>
<td>0.62</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[174]</td>
</tr>
<tr>
<td>Estriol</td>
<td>71</td>
<td>3.1</td>
<td>-</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>[182]</td>
</tr>
<tr>
<td>IL-6</td>
<td>100</td>
<td>3</td>
<td>3</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>[175]</td>
</tr>
<tr>
<td>Combination of fFN, CL</td>
<td>55</td>
<td>3.1</td>
<td>0.5</td>
<td>18</td>
<td>52.4</td>
<td>-</td>
<td>[176]</td>
</tr>
<tr>
<td>Relaxin</td>
<td>58</td>
<td>2.6</td>
<td>0.5</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>[177]</td>
</tr>
<tr>
<td>CL</td>
<td>79</td>
<td>2.3</td>
<td>0.3</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>[178]</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>-</td>
<td>1.3</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[179]</td>
</tr>
</tbody>
</table>

Se = sensitivity, LR+/- = likelihood ratio, FP = false-positive rate, PPV = positive predictive value, NPV= negative predictive value, CL = cervical length, fFN = fetal fibronectin, IL-6 = interleukin-6, CRP = C-reactive protein, CRH = corticotrophin releasing hormone.

Table 5. Ability of selected noninvasive biomarkers to predict PTB in asymptomatic women. (preferably before 37 weeks, if these data not available, other endpoints have been accepted).

<table>
<thead>
<tr>
<th>Marker Combination</th>
<th>Se</th>
<th>LR+</th>
<th>FP</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination, 2 out of 5*</td>
<td>59</td>
<td>24</td>
<td>2</td>
<td>[164]</td>
</tr>
<tr>
<td>Relaxin</td>
<td>27</td>
<td>6.8</td>
<td>4</td>
<td>[180]</td>
</tr>
<tr>
<td>Bishop score ≥ (4)</td>
<td>23.4</td>
<td>-</td>
<td>-</td>
<td>[181]</td>
</tr>
<tr>
<td>fFN</td>
<td>23.4</td>
<td>-</td>
<td>-</td>
<td>[181]</td>
</tr>
<tr>
<td>CL</td>
<td>31.9</td>
<td>-</td>
<td>-</td>
<td>[181]</td>
</tr>
<tr>
<td>Bishop score + CL</td>
<td>14.1</td>
<td>-</td>
<td>-</td>
<td>[181]</td>
</tr>
<tr>
<td>fFN + CL</td>
<td>15.5</td>
<td>-</td>
<td>-</td>
<td>[181]</td>
</tr>
<tr>
<td>CRH</td>
<td>39</td>
<td>3</td>
<td>13</td>
<td>[183]</td>
</tr>
<tr>
<td>G-CSF</td>
<td>49</td>
<td>3.3</td>
<td>15</td>
<td>[184]</td>
</tr>
<tr>
<td>IL-6</td>
<td>20</td>
<td>3.3</td>
<td>6</td>
<td>[185]</td>
</tr>
<tr>
<td>AFP</td>
<td>35</td>
<td>2.6</td>
<td>13</td>
<td>[164]</td>
</tr>
<tr>
<td>CRP</td>
<td>26</td>
<td>1.8</td>
<td>15</td>
<td>[186]</td>
</tr>
<tr>
<td>Estriol</td>
<td>92</td>
<td>-</td>
<td>26</td>
<td>[182]</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>-</td>
<td>1.6</td>
<td>-</td>
<td>[179]</td>
</tr>
</tbody>
</table>

* tested markers: fFN, CL, defensin, α-fetoprotein (AFP), granulocyte colony stimulating factor

Se = sensitivity, LR+/- = likelihood ratio, FP = false-positive rate, CL = cervical length, fFN = fetal fibronectin, G-CSF = granulocyte colony stimulating factor, IL-6 = interleukin-6, AFP = alpha fetoprotein, CRH = corticotrophin releasing hormone, CRP = C-reactive protein.
**Screening of asymptomatic women**

In the absence of major historical or prenatal risk factors, identification of women who will deliver prematurely is difficult. Most women who deliver preterm have no major risk factors, yet more than half of all preterm births occur in apparently low-risk pregnancies. There is a need for a reliable screening test that could identify women at high risk of PTB before symptoms appear. This would allow initiation of early and targeted interventions when they become available. At the moment there is no commercial test available that would fulfill the need. Attempts to screen low-risk women with traditional scoring systems or digital examination have had low sensitivities and low predictive values. Transvaginal ultrasound measurement of cervical length can be used to identify a proportion of asymptomatic women who have an increased risk of preterm birth [66]. Biochemical markers have shown some potential but their performance has been clinically limited (Table 5). An ideal predictive biochemical test for preterm birth would identify women who present with various subtypes of the same condition (i.e. preterm birth attributable to several different etiologies).
Predictive markers

Cervical assessment

Traditionally, the assessment of symptomatic patients for preterm delivery has involved digital (v. lat. digitus, “finger”) examination of the cervix and monitoring of contractions. The classic digital examination assesses the position, effacement, softness, and dilatation of the cervix. All of these parameters are subjective and have high intra- and interobserver variability. Bishop score is a digital scoring system. The total score is achieved by assessing the five components on vaginal examination, cervical dilatation, cervical effacement, cervical consistency, cervical position and fetal station. It is traditionally used to determine how successful an induction of labor might be but in some countries it is also used to predict preterm birth.

Cervical sonography

The most accurate and reproducible method of cervical evaluation is transvaginal ultrasonography (TVU) (Figure 6). Sonographic measurement of cervical length is an established predictor for preterm birth. The shorter the sonographic cervical length, the higher the risk of spontaneous preterm labor/delivery (Figure 7). However there is no agreement on what a sonographic short cervix is. Some investigations have proposed a cut-off of 25 mm while others prefer a cut-off of 15 mm. When using a cut-off of 15 mm at 22 weeks of gestation a subgroup comprising about 1.5 % of the female population at particularly high risk for early preterm delivery was identified [66]. Cervical length measurement is a useful tool but it requires a change in current ultrasound practices. Measurement of cervical length takes about 5 min and it could be carried out at the time of the second scan [67]. Sonographic cervical length is not a comprehensive screening test for spontaneous preterm delivery due to the limitations in the sensitivity of the method. The sensitivity is greater than 50 %, usually 60-80 % [68] meaning that not all women who will have a spontaneous preterm birth have a short cervix at mid-trimester.

Biochemical markers

The term biochemical marker is not well defined. The following definition has been suggested: “a parameter which can be measured in a biological sample and which provides information on an exposure, or on the actual or potential effects of that exposure in an individual or in a group.”

The clinical utility of biochemical markers is that they can give objective results when measured with an accurate test.
Figure 6. Transvaginal ultrasonographic measurement of cervical length.

Figure 7. Association between ultrasonographic cervical length measured at 23 weeks and preterm birth (>32 weeks). [69]
Fetal fibronectin

Fetal fibronectin (fFN) is an extracellular glycoprotein that is thought to act as an adhesive substance, a “tissue glue” between the membranes and the uterine wall. Although it can normally be found in cervico-vaginal fluids it is not commonly found between weeks 26-34. Fetal fibronectin leaks into the vagina if a preterm delivery is likely to occur. It can be measured with a diagnostic immunochromatographic test (Full Term, Hologic, Inc.). The specimen is collected during speculum examination using a swab. The fetal fibronectin test cannot confirm that a woman is in labor, but it can tell if she is not. A negative result with the fFN test means it is highly unlikely that the woman will give birth within the next week or two. A positive result, on the other hand, is not as useful. It means the woman is at a higher risk of giving birth early, but it does not provide an assurance that she is about to give birth, so it will not help the practitioner to decide how to manage the situation. The poor positive predictive value (PPV) of the test is the reason why the fetal fibronectin test is not recommended by the American College of Obstetricians and Gynecologists (ACOG) for routine screening, but only for screening of symptomatic women [70]. The fFN test result may be affected by urine, seminal plasma or blood, and is not indicated if the membranes have ruptured.

Ph-IGFBP-1

Phosphorylated insulin-like growth factor binding protein (phIGFBP-1) is a protein secreted by decidual cells. When the delivery is approaching, fetal membranes begin to detach from the decidua and phIGFBP-1 leaks into cervical secretions. Detection of phIGFBP-1 in cervical secretions of symptomatic patients is a marker for prediction of preterm delivery. phIGFBP-1 can be measured with a commercial rapid immunochromatographic test (Actim Partus, Medix Biochemica). The test result is not affected by urine or seminal plasma but maternal blood may interfere with the assay. The strength of the test is the high negative predictive value (NPV). A negative phIGFBP-1 indicates a very low risk of PTD and thus that there is no need for additional care beyond the antenatal care program.

Estriol

Estriol (E3) is a naturally occurring derivative of the hormone estrogen. There is a surge in salivary estriol several weeks prior to the onset of spontaneous preterm labor. Therefore, measurement of salivary estriol has been explored as a risk predictor for preterm labor. SalEST™ is a laboratory technique for measuring salivary estriol levels. The method is not satisfactory. For example, ACOG does not recommend the salivary estriol test as a screening test for
premature labor because it produces a high percentage of false positive results and could potentially add significant costs and unnecessary interventions to prenatal care [71]. The positive predictive value of a salivary estriol test is only about 20%, (the negative predictive value is about 98%) [72]. Furthermore, salivary estriol predicts late preterm birth quite well, but it is not especially useful for the prediction of earlier preterm births [197].

**Combination of markers**

Many markers have been reported to be associated with preterm birth. However, few have demonstrated sufficiently good predictive value when used alone. Today’s data strongly suggests that a single predictive marker effectively accounting for a large proportion of premature delivery is unlikely to be found simply because of the multifactorial etiology of PTB. Combination of non-overlapping biochemical markers may considerably improve the success of any individual marker to predict PTB.

Combination of biochemical markers, cervical length and previous obstetric history may provide a useful screening tool [163, 164] (Figure 8). Several studies have tested the effect of a combination of potential markers for predicting PTB and some of them have shown improved performance (Table 6.).

![Figure 8](image.png)

**Figure 8.** Risk of spontaneous PTB at various gestational ages with various combinations of risk factors in nulliparas and multiparas. [164]
Table 6. Examples of combinations of markers for predicting PTB.

<table>
<thead>
<tr>
<th>Women (n)</th>
<th>Primary outcome</th>
<th>Test</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>PTB &lt;35 w</td>
<td>philGFBP-1</td>
<td>67.0 %</td>
<td>83.0 %</td>
<td>27.0 %</td>
<td>96.0 %</td>
<td>[165]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL ≤ 30 mm</td>
<td>100.0 %</td>
<td>45.0 %</td>
<td>15.0 %</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>philGFBP-1 + CL 20-30 mm</td>
<td>75.0 %</td>
<td>74.0 %</td>
<td>23.0 %</td>
<td>97.0 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>philGFBP-1 + CL &lt;20 mm</td>
<td>60.0 %</td>
<td>77.0 %</td>
<td>50.0 %</td>
<td>83.0 %</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>PTB Within 7 d</td>
<td>philGFBP-1</td>
<td>83.3 %</td>
<td>84.4 %</td>
<td>41.7 %</td>
<td>97.4 %</td>
<td>[166]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fFN</td>
<td>83.3 %</td>
<td>80.0 %</td>
<td>35.7 %</td>
<td>97.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL ≤ 20 mm</td>
<td>66.7 %</td>
<td>95.6 %</td>
<td>66.7 %</td>
<td>95.6 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL ≤ 25 mm</td>
<td>66.7 %</td>
<td>88.9 %</td>
<td>44.4 %</td>
<td>95.2 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>philGFBP-1 + CL &lt;20mm</td>
<td>80.0 %</td>
<td>97.3 %</td>
<td>80.0 %</td>
<td>97.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fFN + CL &lt;20mm</td>
<td>80.0 %</td>
<td>97.2 %</td>
<td>80.0 %</td>
<td>97.2 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>philGFBP-1 + CL &lt;25mm</td>
<td>80.0 %</td>
<td>97.1 %</td>
<td>80.0 %</td>
<td>97.1 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fFN + CL &lt;25 mm</td>
<td>80.0 %</td>
<td>97.0 %</td>
<td>80.0 %</td>
<td>97.0 %</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>PTB &lt;32 w</td>
<td>1 out of 5 markers* +ve</td>
<td>92.7 %</td>
<td>65.9 %</td>
<td>-</td>
<td>-</td>
<td>[164]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 out of 5 marker +ve</td>
<td>58.5 %</td>
<td>97.6 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 out of 5 marker +ve</td>
<td>19.5 %</td>
<td>100 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum only**</td>
<td>80.5 %</td>
<td>78.1 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>PTB&lt;37 w</td>
<td>CRH</td>
<td>24 %</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[169]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFP</td>
<td>25 %</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFP + CRH + risk factor score</td>
<td>37 %</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>PTB&lt;37 w</td>
<td>CL ≤ 26 mm</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>89.1</td>
<td>[176]</td>
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<td></td>
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<td>fFN</td>
<td>-</td>
<td>-</td>
<td>45.2</td>
<td>86.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL + fFN</td>
<td>-</td>
<td>-</td>
<td>52.4</td>
<td>94.4</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>PTB&lt;37 w</td>
<td>IL-6</td>
<td>73 %</td>
<td>61 %</td>
<td>-</td>
<td>-</td>
<td>[170]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-8</td>
<td>64 %</td>
<td>55 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>philGFBP-1</td>
<td>48 %</td>
<td>68 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL &lt;29.3 mm</td>
<td>82 %</td>
<td>48 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-6 + IL-8 + cervical index 0.36</td>
<td>30 %</td>
<td>97 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-6 + IL-8 + cervical index 0.36 + philGFBP-1</td>
<td>10 %</td>
<td>98 %</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*tested markers: fFN, CL, defensin, α-fetoprotein (AFP), granulocyte colony stimulating factor
** Serum only = result considered as positive if any serum marker, defensin, α-fetoprotein or granulocyte colony stimulating factor, was positive.
Potential future biomarkers

Cytokines

Cytokines have been investigated as protein biomarkers of impending premature delivery. Cytokines are low-molecular weight glycoproteins that mediate the activation of immune cells and coordinate the production and secretion of antibodies and other cytokines. They also stimulate uterine contractions via the production of prostaglandins and perhaps cause preterm cervical ripening and PPROM via stimulation of metalloproteinases [73]. Elevation of pro-inflammatory cytokines in maternal serum and cervicovaginal fluids during infection and before parturition has been extensively described. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and TNF-α protect the host against invading microorganisms [74]. In addition to protective effects this response can also be harmful to the host. For this reason the pro-inflammatory immune cascade is tightly regulated. Resolution of the inflammatory process and healing occurs through the activity of anti-inflammatory cytokines such as interleukin-receptor antagonist. An imbalance between pro- and anti-inflammatory response has been implicated in the pathogenesis of infection related premature birth [75]. Preterm birth has been associated with elevated levels of IL-1, IL-6 and IL-8 cytokines even in the absence of signs of intrauterine infection [51].

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are responsible for the turnover and degradation of connective tissue proteins. MMPs affect the activity of various cytokines, indicating dual role for MMPs in the activation and inactivation of the inflammatory system. MMPs are involved as proteolytic enzymes in preterm labor and PPROM as well as in pre-eclampsia, intrauterine growth restriction, chronic lung disease, necrotizing enterocolitis, intraventricular hemorrhage, cystic periventricular leucomalacia and retinopathy of prematurity [188]. MMP-9 is involved in the degradation of the basement membrane and other extracellular matrix components and increase in humans at the time of parturition [76]. Maternal serum MMP-9 concentration raises 24 h before the initiation of labor. Such late prediction is of little value in allowing initiation of preventive steps, but can aid in understanding the mechanisms of PTB [77]. Recent studies suggest that increased fetal levels of MMP-9 are involved with PPROM and differentiate fetuses with PPROM from those undergoing premature labor with intact membranes [46]. Thus, it has been questioned whether PPROM is simply an accident or whether a sick fetus may initiate preterm parturition by activating the mechanisms responsible for rupture of membranes. The teleologic advantage of the latter would be a more rapid exit from a hostile environment. Alterations in
the concentrations of other MMPs (MMP-1, -2, -3, -7, -8, -12, -13 and -14) have also been associated with preterm birth. Since MMPs are involved in the perinatal complications of prematurity they are thus potential targets for therapeutic intervention [188].

**Relaxin**

Relaxin is a collagenolytic hormone that causes increased production of the matrix metalloproteinases. Decidual expression of relaxin is increased in patients with PPROM. Relaxin causes increase in expression MMP-1, MMP-3 and MMP-9. Local relaxin could therefore cause activation of specific enzyme cascade resulting in degradation of membranes [168].

**Stress related biomarkers**

Empirical evidence, based on prospective population-based studies provide substantial support for the premise that infants of mothers experiencing high levels of psychological or social stress during pregnancy are at significantly increased risk for preterm birth and low birth weight. Stress is known to evoke a variety of adaptational responses, including stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Several studies have shown elevated levels of placental corticotrophin releasing hormone, CRH to be implicated in spontaneous preterm birth. Stress-related physiological responses may thereby contribute to adverse birth outcomes. Evidence suggests that chronic stress is associated with immunosuppression. Maternal stress and infection are risk factors in premature birth. However, the nature of the stress-immune system relationship has been little studied in human pregnancy. Women at risk for spontaneous preterm delivery may possibly be identified solely by stress related biomarkers e.g., CRH, cortisol and urocortin, obtained from maternal blood in early pregnancy. Urocortin is a member of the CRH family and according to recent studies its measurement in maternal plasma suggests it may have potential as a new biochemical marker of PTD [78].

**Endocannabinoids**

Endocannabinoids are substances produced within the body, which activate cannabinoid receptors. Anandamide (N-arachidonylethanolamine) was the first endocannabinoid discovered. In recent years it has been demonstrated that high circulating levels of this endogenous cannabinoid, as a result of low expression of its metabolizing enzyme, fatty acid amide hydrolase (FAAH), may contribute to spontaneous miscarriage [79]. Endocannabinoids and fatty
acid amide hydrolase have been found to have a potential role in signaling for implantation and maintenance of pregnancy. Abnormal secretory endometrial changes may adversely affect early pregnancy outcome [80]. The roles of endo-
cannabinoids and agents modulating their receptors are potentially very ex-
citing areas to be explored further.

PAPP-A

Pregnancy associated plasma protein A (PAPP-A) is a glycoprotein which is se-
creted from the trophoblastic tissues of the placenta. Decreased levels of PAPP-A can be seen in pregnancies affected with Down syndrome in the first trimester of the pregnancy. Low levels of maternal serum PAPP-A have been shown to be associated, in the absence of an abnormal karyotype, with an increased risk of preterm or early preterm delivery [200]. Low maternal serum PAPP-A levels during the first trimester may reflect a trophoblast invasion defect in the maternal-fetal interface, resulting in subsequent preterm delivery, particularly in the case of PPROM [201].

sFlt1, sEng and PIGF

Pre-eclampsia is accompanied by elevated maternal serum concentrations of angiogenic factors such as soluble fms-like tyrosine kinase (sFlt1), soluble endo-
glin (sEng) and reduced levels of free placental growth factor (PIGF). A modest increase in maternal sFlt1 and sEng and decreases in free PIGF have been found to be associated with preterm birth [204].

Fetal cells and fetal cell-free DNA

There is a certain degree of fetal-maternal transfusion in every pregnancy. Feto-maternal cell trafficking has long been associated with pre-eclampsia. Subsequent studies have shown that changes in fetal cells, and more recently cell free fetal nucleic acids may also occur in other pregnancy related disorders including preterm labor, intra-uterine growth retardation, hyperemesis gravidarum or even pregnancies at high altitude. Theoretically all new and paternal inherited disorders with a known gene defect can be detected in maternal plasma. Small scale studies have described elevated concentrations of free fetal DNA in maternal plasma in (threatening) preterm labor, pre-eclampsia and aneuploidy. Large-scale studies are necessary to demonstrate the value of these findings [202]. According to the studies, preterm labor seems to be associated with an elevated release of cell free fetal nucleic acids only but not with an increment in feto-maternal cell trafficking [203].
Genetic polymorphism

Well-established observations support a genetic influence on the risk of premature birth. Many studies have found associations between single nucleotide polymorphisms (SNP) in cytokine genes responsible for inflammation in women who experienced premature birth (Table 7). However most studies lack sufficient power to make strong associations. Polymorphisms in the TNF-α, IL-6 and IL-4 genes as well as other inflammatory mediators have been reported. Fetal polymorphisms have also been evaluated. Candidate gene studies can be used in premature birth to understand the contribution of DNA polymorphism/genetic predisposition to disease risk. SNP analysis may reveal opportunities even for pre-pregnancy testing for premature birth. Besides developing assays for these SNP genotypes one of the major challenges is to investigate further the molecular mechanisms behind already established SNPs associated with premature birth.

Table 7. Studies about genetic polymorphisms associated with PTB

<table>
<thead>
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<th>Symbol</th>
<th>Publications</th>
<th>(Ref)</th>
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<tr>
<td>Interleukin 1 α</td>
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<td>IL1B</td>
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<td></td>
<td>Moore 2004</td>
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<td></td>
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<td>Annells 2004</td>
<td>[81]</td>
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<tr>
<td></td>
<td></td>
<td>Genc 2002</td>
<td>[84]</td>
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<tr>
<td>Interleukin 1 receptor antagonist</td>
<td>IL-1RN</td>
<td>Murtha 2006</td>
<td>[85]</td>
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<td></td>
<td></td>
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<td>Epoxide hydrolase</td>
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<td>Wang 2001</td>
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Cervicovaginal markers

A case-control proteomic study identified several proteins with greater differential expression than fFN when comparing an asymptomatic group and a symptomatic group. Among these proteins were calgranulins, annexins, S100 calcium binding protein A7, α-1 acid glycoprotein, and α-1 antitrypsin precursor. Further characterization of these markers in a large cohort of subjects may provide the basis for a new test for early, noninvasive prediction of PTB. [205]
Prevention

For many years the interventions for the prevention of preterm birth have been reactive rather than proactive and have been associated with poor results. A delay of a few days in the delivery is often associated with a significant increase in survival. Delaying delivery may reduce the rate of long-term morbidity by facilitating the maturation of developing organs and systems. There is conflicting evidence as to how to manage such patients effectively and further research is needed in this field.

Traditional recommendations

Bed rest, hydration and pelvic rest have been standard recommendations for women at risk or receiving tocolysis for PTL. None of these has been shown to be effective. [23]

Home uterine monitoring

Home uterine monitoring (HUAM) has been studied as a method of closely observing uterine activity and thus enabling intervention in a timely manner. A lightweight, portable patient unit includes a sensor (i.e., tocodynamometer) and a device for recording, storing and transmitting data picked up by the sensor. The practitioner analyzes the data along with the patient’s reported symptoms and advises the patient on her status and recommended course of action [234]. Research has not shown a clear advantage of home monitoring. [124]

Cerclage

The traditional intervention for women with recurrent preterm deliveries or second trimester losses is cervical cerclage. Cervical cerclage is a surgical procedure, in which the cervix is sewn closed during pregnancy. It was introduced in 1955 by Shirodkar [144], yet remains one of the more controversial surgical interventions in obstetrics [145]. A closed cervix helps a developing baby stay inside the uterus until the mother reaches 37-38 weeks of pregnancy.

The cervix is the lowest part of the uterus and extends into the vagina. During normal pregnancy it remains closed until the third trimester. The stitch is removed when it is time for the baby to be delivered. Cervical cerclage has been widely used to prevent early preterm birth when a woman’s cervix is weak (sometimes called cervical insufficiency/incompetence). If a woman has a cervical insufficiency she is more likely to have a baby born prematurely because the cervix shortens or opens too early. When the cervix is healthy, it thins out
and opens at the end of pregnancy when labor begins. With cervical insufficiency, the cervix opens without labor. The woman may deliver the baby without feeling contractions. The diagnosis of cervical insufficiency is notoriously difficult. There is no objective diagnostic test and the diagnosis is usually a retrospective one.

There are five different techniques for performing the cerclage. These are either vaginal or abdominal. The two most common are the McDonald procedure and Shirodkar operation.

1. McDonald procedure
2. Shirodkar operation
3. Wurm procedure (Hefner cerclage)
4. Transabdominal cerclage
5. Lash procedure.

Currently, three categories of patients with cervical insufficiency can be defined. Prophylactic or elective cerclage is performed on those women with classic historical features of cervical insufficiency, i.e. those with two or more second trimester losses lacking bleeding or clear signs of labor preceding the loss. The second category is urgent cerclages that are performed on asymptomatic women where digital or ultrasonographic examination reveals a short cervix or funneling. The third category includes women with clear signs of cervical dilation and significant effacement but no uterine contractions. These women are candidates for nonelective emergency cerclage.[146]

Cervical cerclage is not without risk. Reported adverse effects shortly after suture insertion include abdominal pain, vaginal bleeding, PPROM and bladder injury. Late complications can include infections such as chorioamnionitis. Obstetrically, cervical cerclage is contraindicated in the presence of uterine contractions, PPROM, fetal demise and congenital lethal malformations.

Despite cervical cerclage being a relatively common operative procedure, there is still little evidence as to its efficacy. The probability of it being of benefit is highest in women with a very high risk of PTB. Since there are relatively few complications, it is likely that cerclage will continue to be offered to women with clear cervical insufficiency. Some clinicians base the decision to insert cervical cerclage on an ultrasonographic short cervical length. Serial cervical ultrasound examinations with cerclage insertion only if indicated, has been suggested to be a reasonable practice, as most women treated with cerclage do not need it [145, 147].
In low risk women (based on obstetric history) with a short cervix (< 15 mm), cerclage does not appear to reduce the risk of PTB probably due to the association with visible fetal membranes [48]. The evidence is conflicting as to whether cerclage is beneficial once the pathological process has begun and cervical shortening is seen and at what cervical length to intervene. The efficacy of cerclage can vary according to the cause of the short cervix. Sakai et al. found that women with an elevated concentration of IL-8 in cervical secretions and short cervix may not benefit from cerclage. These patients may have an inflammatory or infection related process ongoing and cerclage does not help or it may even be harmful [49, 50]. These results suggest that cerclage will only be beneficial if the shortening happened in the absence of inflammation. Therefore identification of patients who can benefit from cerclage cannot be made based on obstetric history or cervical ultrasound alone. Combination of IL-8 concentration measurement from cervical secretions, sonographic measurement of cervical length and obstetric history is more likely to identify patients who would most benefit from cerclage to prevent PTB [5]. Until such a diagnosis can be made, cerclage should be reserved for patients with anatomic insufficiency [62].

**Antibiotics**

Infection may be an important cause of PTB. Antibiotic use for prenatal prophylaxis of preterm labor and membrane rupture and for prevention of preterm birth in women in preterm labor has been widely debated for more than 30 years. Different antibiotics (e.g. clindamycin, metronidazole and erythromycin) with varying doses and by different routes have been administered to women at a range of gestational ages with differing risks of PTB. This has, not surprisingly, resulted in different results. In these studies, about a third have suggested that antibiotic regimens are beneficial in reducing preterm birth, while the rest have not. In contrast, other studies have shown that in some populations, the use of antibiotics has been associated with an increase in preterm births [126, 127]. Romero et al. have proposed that preterm labor is a complex syndrome and that many factors other than infection may be involved. Therefore antibiotic administration as a preventive strategy is destined to fail, or even cause harm, if we assume that infection is the only cause of preterm labor [128].

Early PTB is strongly associated with infection. Early detection of abnormal flora (even if this returns to normal) is associated with a greater risk of adverse events rather than late detection. Therefore, the conception of today is that, if they are to be effective antibiotics, they should be used early in pregnancy before inflammatory feto-maternal tissue damage occurs. Prophylactic use of antibiotics is more likely to be successful if only used in women at risk of PTB.
due to infection or abnormal flora, or in women with a predisposition to mount a damaging inflammatory response to infection. [129]

**Can antibiotic treatment of bacterial vaginosis prevent or delay preterm birth**

Bacterial vaginosis, both symptomatic and asymptomatic has in numerous studies been associated with poor perinatal outcome; in particular an increased risk of preterm birth. The treatment of bacterial vaginosis in women at low risk for preterm birth is not recommended today and whether it is effective in high-risk patients is subject to debate.

**Progesterone**

The female hormone progesterone has been used to prevent preterm birth. The first trial of progestational agents (of which progesterone is one) for the prevention of preterm birth in women at increased risk was published in 1970 by Papiernik. The exact mechanism of progesterone in the prevention of preterm birth is still not fully understood, though, for example, progesterone has been shown to be responsible for myometrial quiescence in vitro by inhibiting myometrial contractions, blocking effects of oxytocin by inhibiting formation of gap junctions [130]. The evidence accumulated until the 1990s was fraught by mixed results, and was based on mostly underpowered studies with variable eligibility criteria. When the available randomized, placebo controlled trials were analyzed in a meta analysis in 1989 no reduction in the risk of PTB could be confirmed [131]. Another analysis using the same studies but different criteria found a 50 % reduction in PTB but no significant reduction in death or disease was observed [132]

Two recent studies from the United States [133] and Brazil [134] have re-awoken the interest in progesterone supplementation. Both of these studies showed a statistically significant reduction in the incidence of PTB by about 50-60 % among women with a history of preterm birth. The studies used different progestational agents and different administration routes. The NICHD trial (National Institute of Child Health and Human Development), conducted in the United States, used weekly intramuscular administration of synthetic progesterone, 17 alpha hydroxyprogesterone caproate (17P), initiated before 21 weeks gestation whereas in the Brazilian study women were treated prophylactically with vaginal natural progesterone suppositories. Neither study showed a reduction in the incidence of spontaneous preterm birth suggesting that progesterone may sensitize the uterus to tocolytics, which subsequently prevent PTB rather than prevent preterm labor by itself.
Today, progesterone therapy is thought to be a promising, cost efficient intervention for women at high risk of recurrent preterm birth. Bailit and Votruba (2007) concluded that treating expectant mothers with a prior spontaneous preterm birth with 17P would generate future medical cost savings that substantially exceed the cost of treatment. According to their calculation, if the eligible population were universally treated, discounted lifetime medical costs of their offspring could be reduced by more than $2.0 billion annually [36].

Several studies have recently been conducted to find an optimal progesterone formulation, administration route, timing and indication (Table 8).

Table 8. Summary* of recent progesterone studies.

<table>
<thead>
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<th>Author [Ref]</th>
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<th>Primary outcome</th>
<th>Outcome in treated group</th>
<th>Outcome in control group</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n)</td>
<td>Criteria</td>
<td>women</td>
<td>PTB</td>
<td>5/23 (55 %)</td>
<td>12/22 (22 %)</td>
</tr>
<tr>
<td>Facchinetti (2007) [141]</td>
<td>IM 17P (250 mg)</td>
<td>Singleton: undelivered after episode of preterm labour</td>
<td>PTB &lt; 37 wks</td>
<td>135/325 (42 %)</td>
<td>123/330 (37 %)</td>
</tr>
<tr>
<td>Rouse (2007) [135]</td>
<td>IM 17P (250 mg)</td>
<td>Twin pregnancy</td>
<td>PTB &lt; 35 wks</td>
<td>2/72 (2.8 %)</td>
<td>13/70 (18.6 %)</td>
</tr>
<tr>
<td>Fonseca (2003) [134]</td>
<td>Vaginal natural progest. (100 mg)</td>
<td>Singleton pregnancies with history of PTB</td>
<td>PTB &lt; 34 wks</td>
<td>90/306 (29.4 %)</td>
<td>69/153 (45 %)</td>
</tr>
<tr>
<td>Meis (2003) [133]</td>
<td>IM 17P (250 mg)</td>
<td>Singleton pregnancies with history of PTB</td>
<td>PTB &lt; 37 wks</td>
<td>24/125 (19.2 %)</td>
<td>43/125 (34.4 %)</td>
</tr>
<tr>
<td>Fonseca (2007) [66]</td>
<td>Vaginal natural progest. (200 mg)</td>
<td>Singleton/twin pregnancies</td>
<td>PTB &lt; 34 wks</td>
<td>24/125 (19.2 %)</td>
<td>43/125 (34.4 %)</td>
</tr>
<tr>
<td>O’Brien (2007)</td>
<td>Vaginal natural progest. (90 mg)</td>
<td>Singleton, history of PTB or mid trimester CL shortening</td>
<td>CL changes</td>
<td>CL shortening significantly less than in placebo group</td>
<td>P = 0.038</td>
</tr>
</tbody>
</table>

IM= intra muscular, ns= not significant
*Randomisation to progesterone only if CL < 15 mm at > 20 weeks’ gestation.
*Acknowledgements to Dr Manju Chandiramani and Dr Rachel Tribe, King’s College London, UK.
The effect of supplemental progesterone compounds is not universal in women with previous PTB, indicating that some pathways to PTB are not influenced by this therapy. For example, in a study of women with a short cervix, treatment with natural progesterone was successful in reducing the rate of spontaneous early preterm delivery [66] whereas synthetic 17P had no effect on women with twin pregnancies [135]. This suggests that the effect of progesterone might be related to modulation of inflammation or cervical ripening rather than to uterine contractility [162]. There is still uncertainty whether treatment with progestational agents can also reduce the risk of perinatal and neonatal mortality. This evidence is essential before recommending the treatment, as there is always the potential risk of unanticipated adverse effects from fetal exposure to hormonal or other medical therapies. The American College of Obstetricians and Gynecologists (ACOG) recommends that the use of progesterone supplementation in pregnancy to prevent PTB should be restricted to women with a documented history of prior spontaneous PTB [140].

Safety of synthetic 17P and natural progesterone

During the 1950s and 1960s synthetic progestins were frequently administered to pregnant women, e.g. for treatment or prevention of miscarriage. With the thalidomide tragedy in the 1960s, all pharmaceuticals became suspect as to their potential for unanticipated adverse effects on fetal development. Some progestins had been thought to be associated with masculinization and malformation of the fetus [155, 156] and considerable concern was raised regarding their use. In response to these concerns the US FDA required a warning label on all progestational agents stating that there was an increased risk of birth defects if taken during the first 4 months of pregnancy. The warning was removed in 1999.

A recent extensive literature search has again raised concerns about the safe use of synthetic 17P in the prevention of preterm birth. It revealed that there was a signal for embryo-fetal toxicity associated with 17P in the two largest clinical trials conducted to date, the NICHD-study being one of them [137, 133, 154]. Despite their positive interest, the NICHD-study results also included a warning that the synthetic progesterone 17P may be associated with an increase of miscarriage and stillbirths. The study was followed by an FDA requested, four year follow up study of children exposed to 17P in utero, but this time the researchers did not notice any difference between the 17P exposed children and the placebo children [153]. Recently, a retrospective analysis by Rebarber et al. 2007 emphasized the importance of continuation of treatment with 17P because early cessation of 17P was found to be associated with an increased risk of preterm delivery [138]. Rebarber has also found an association between the use of 17P for the prevention of recurrent preterm delivery with an increased risk of
developing gestational diabetes mellitus [139]. Another problem with 17P is its preparation using castor oil (a vegetable oil obtained from the castor bean). The FDA withdrew approval for manufacturing castor oil by pharmaceutical companies but compounding pharmacies are still permitted to prepare 17P using castor oil. Some have speculated that the castor oil in the formulation may not be beneficial to pregnancy [155].

Natural progesterone seems to be a safe option according to a large study made by the Fetal Medicine Foundation Second Trimester Screening Group in 2007. No serious adverse events associated with the use of vaginally administered natural progesterone were found [66].

Unresolved issues regarding progesterone therapy:

- **What is the optimal progesterone formulation (synthetic or natural)?**
- **What is the optimal route of administration (injections, vaginal administration)?**
- **Has the long-term safety of these drugs been established?**
- **There is no FDA approved drug available for PTB indication.**

**Nutritional supplementation**

The mother’s nutritional status has an impact on pregnancy outcome. For example low serum folate, iron or zinc levels during pregnancy are thought to be associated with an increased risk of preterm birth [142, 194, 195]. Malone et al (2007) reported that preconceptional folate supplementation is associated with a 50-70% reduction in the incidence of early preterm birth [158]. Also low consumption of seafood has been reported to be associated with premature birth [143]. According to a French study, different categories of seafood may be differently associated with birth outcomes. Fish consumption was found to be associated with increased length of gestation and shellfish consumption with decreased fetal growth [159]. Although the evidence for the use of fish oils to prevent PTB is strong, particularly in women with poor fish oil intake who are at risk of PTB, recommendations on the dosage of omega-3 and the timing, and on the profiling of subjects require further research. Nutritional supplementation has a role in helping the mother to receive those substances that her diet may lack. The role of nutrient supplementation in women with a well-balanced diet that already provides all necessary nutrients, vitamins and minerals is less clear. There are many potential mechanisms by which maternal nutritional status might affect preterm birth. Thin women may have decreased blood volume and reduced uterine blood flow. Obese women are more likely to have congenital anomalies and their infants are more likely to be delivered preterm [196]. Also obese women are more likely to develop pre-eclampsia and diabetes, with iatrogenic preterm birth indicated by these conditions.
Diagnosis and Management

The mechanism of human parturition is not known and currently there are no methods for predicting when women will go into labor at term, let alone preterm labor. Once the threat of preterm labor is established clinicians may attempt to stop or attenuate uterine contractions using tocolytic drugs. However about half of women receiving placebo therapy do not deliver within a week from the start of therapy. In other words, either the diagnosis of preterm labor is wrong or the threat of preterm labor neutralizes naturally and the uterus returns to a quiescent state. These questions may not be resolved until the physiological mechanism of parturition is fully understood.

There is no evidence that tocolytics can prolong pregnancy for sufficient time to improve perinatal outcome, however many clinicians use tocolytics to achieve short-term gains such as enabling the transfer of the mother to a tertiary referral centre with good obstetric and neonatal facilites, or gaining time to administer glucocorticoids to improve fetal lung maturation. Nevertheless, it must be emphasized that many episodes of threatened preterm labor are false alarms and some women are treated unnecessarily.

Diagnosis

The diagnosis of preterm labor is made when a woman between 22 and 37 weeks gestation presents with persistent uterine activity (contractions, at least one every 10 minutes or more often) and progressive cervical changes (> 2 cm dilatation; > 80% shortening), with or without premature rupture of the membranes or some vaginal bleeding. Initial investigations include an assessment of fetal heart rate (cardiotocography); speculum examination or digital examination (depending on the state of the membranes) for cervical assessment and high vaginal swabs for microbiology. An evaluation should be made of possible predisposing factors, e.g. fetal abnormalities, placental abruption, intrauterine infection.

The presence of uterine contractions alone cannot be used to diagnose preterm labor because often it is difficult to distinguish true uterine activation that is going to lead to preterm delivery from Braxton Hicks contractions that occur in numerous pregnancies that deliver at term. The diagnosis must be supported by evidence of progressive changes in the uterine cervix. Some patients may present without contractions, but with a dilated cervix (silent cervical dilatation). If the cervical length is $\geq 30$ mm the woman is unlikely to be in preterm labor, especially if the fetal fibronectin test is negative. On the other hand the presence of progressive and advanced cervical changes is a strong indicator of true preterm labor and the risk of delivery increases with decreasing cervical length.
(< 25 mm), especially if there is “funneling” of the cervix as the fetal membranes penetrate the cervical canal.[215] [216]

The correct diagnosis of PPROM is important, because it influences the management of preterm labor, even though it is not always associated with it. Persistent loss of clear fluid per vagina is diagnostic in a high percentage of cases, however loss of urine or excessive production of vaginal fluid may be mistaken for amniotic fluid. Sometimes there can be loss of clear fluid as a consequence of cervical incompetence without true rupture of the membranes. Changes in vaginal pH can help in the diagnosis of ruptured membranes; during pregnancy vaginal pH is acidic (4.5 or lower) but it turns alkaline in the presence of amniotic fluid. However the presence of seminal fluid or some vaginal infections that increase the pH can give false positives. Persistent loss of amniotic fluid, can lead to oligohydramnios (too little fluid in the uterine cavity). Some clinicians advocate amnioinfusion in early PPROM to try to prevent fetal pulmonary hypoplasia secondary to oligohydramnios. All cases of PPROM require careful monitoring, independent of uterine activity, because of the risk of ascending vaginal infection. Signs of infection (clinical chorioamnionitis) include elevated temperature (≥ 38.5 °C), maternal tachycardia, high white blood cell count, uterine tenderness and foul smelling vaginal discharge. However sub-clinical infection may be difficult to detect. [217]

Management

The diagnosis of preterm labor is very difficult before advanced cervical dilatation and repeat vaginal examinations may be required to ascertain progressive cervical changes. This is important in order to minimize the unnecessary treatment of women who are not in preterm labor. Once the diagnosis of preterm labor is firmly established, the benefits of trying to prolong the pregnancy must be weighed against the risks of fetal or maternal side-effects. The most important factor in the management of preterm labor is gestational age. After 34 weeks there is no measurable benefit for the baby and most clinicians will not attempt to stop labor. From 28 to 34 weeks prolonging pregnancy will decrease significantly perinatal morbidity. At less than 28 gestation gaining a few weeks or even a few days is associated with a significant improvement in perinatal morbidity and mortality. The management of threatened preterm labor at less than 24 weeks gestation is extremely difficult requiring careful consideration of the risk of serious long term disability in the surviving infants.

If the presence of active preterm labor is confirmed with persistent uterine contractions, cervical effacement of more than 80% and progressive cervical dilatation reaching 3-5 cm, the management involves bed rest and psychological reas-
surance of the patient. The relatives must be informed. Of the risks tocolytics to inhibit uterine contractions and corticosteroids to induce lung maturation may be given (see below). At this stage it is important to contact the pediatrician to prepare neonatal support or, if this is not available locally, a decision has to be made about transporting the patient to a tertiary referral centre with good neonatal facilities. If there is no PPROM the prophylactic use of antibiotics is not recommended [218]. If the episode of preterm labor is associated with PPROM and/or if there are any signs of bacterial colonization, e.g. by group B streptococcus the use of antibiotics is recommended. The choice of antibiotic is not clear and some studies have warned against the use of co-amoxiclav in women at risk of preterm delivery because of a possible link with neonatal complications such as necrotizing enterocolitis [219].

If after 48 hours of tocolytic treatment uterine activity remains inhibited and there are no further cervical changes, the treatment may be stopped and the patient will either continue with the pregnancy and deliver at term or return with another episode of preterm labor, which will need to be treated again.

If contractions persist despite treatment (3 or more every 10 minutes) and the cervix is fully effaced with ≥ 5 cm dilatation the possibilities to stop labor are minimal and efforts should concentrate on making the delivery as safe as possible, bearing in mind that in advanced preterm labor delivery can occur very rapidly. Although referral to a tertiary hospital is desirable, transfer is not indicated if there is imminent risk of delivery [220].

The preterm fetus is less able to cope with asphyxia or birth trauma than a fetus at term so extra care is necessary to minimize these risks, especially in breech presentations, which are more common in preterm labor than in labor at term. If the presentation is cephalic, vaginal delivery is the preferred route. In breech presentations there is controversy as to whether vaginal or caesarean delivery should be the method of choice [221].

Fetal monitoring during the dilatation stage will include electronic recording of the fetal heart rate, and when indicated, fetal blood sampling for gases and pH to diagnose hypoxia. Epidural analgesia is the ideal form of pain relief during labor and delivery because it avoids the risk of systemic drug depression in the preterm newborn. The general guidelines for term vaginal deliveries apply to preterm deliveries, but it is important to minimize trauma. Ventouse deliveries should be avoided, especially in very preterm infants, to avoid the risk of intracranial hemorrhage.

There are no differences in the indications for caesarean section between term and preterm deliveries, however the lower uterine segment is narrower in the
preterm uterus and the surgical technique is more demanding. It is important to deliver the preterm fetus with minimal trauma and sometimes a longitudinal rather than a transverse incision has to be performed to create enough space for a safe delivery. Surgical complications (bladder damage, broad ligament tears) are more common in preterm caesarean sections than at term.

Ideally, before delivery a neonatologist should be alerted and the parents should be counselled and involved in any plans for resuscitation of the baby. Whether delivery is vaginal or by caesarean section, the presence of an experienced neonatologist to provide immediate care under the best possible conditions are essential to improve the outcome of the newborn.[222]

Emergency cerclage

The decision to perform an emergency cerclage as part of the management of preterm labor in women with advanced cervical effacement and dilatation but no contractions (cervical incompetence) requires careful consideration on an individual basis. The operation may prove to be technically difficult and may provoke membrane rupture [223, 224].

Corticosteroids

A baby that is born very early is at risk of breathing difficulties (respiratory distress syndrome). A single course of corticosteroids, given to a woman who may give birth early, helps develop her baby’s lungs. However, this benefit does not last beyond seven days. It is not clear whether there is benefit in repeating the dose of prenatal corticosteroids for women who remain at risk of preterm birth after an initial course. According to Crowther and Harding repeat doses of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life [160]. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks [160, 161].

Tocolytics

Tocolytics are medications used to suppress premature labor. They are given to gain time for administration of corticosteroids, which greatly accelerate fetal lung maturity, but take one to two days to work. Another goal of tocolytic therapy is to allow transportation of the mother to a tertiary care center. Delaying delivery may reduce the rate of long-term morbidity by facilitating the maturation of developing organs and systems. Tocolytics are not without risk to the mother and fetus. Typical side effects are nausea and headache.
Beta agonists and calcium channel blockers may cause problems with heart rhythm.

For these reasons tocolytics must be reserved for women with real risk of PTB and not given prophylactically to asymptomatic women or to women whose contractions are not true labor contractions. Various types of agents are used, with varying success rates and side effects. The choice of tocolytic agent for treating PTL is based on local experience and availability. All of the medications prolong pregnancy beyond 48 hours. The use of tocolytic therapy in an attempt to reduce preterm delivery has not reduced the overall preterm birth rate [25]. Although tocolytic treatment is the standard of care, there is no FDA approved drug for therapy, and there is no unanimity of drug regimens among physicians.

- **Beta agonists** - ritodrine, terbutaline, salbutamol, isoxuprime
- **Calcium channel blockers** - nifedipine
- **Prostaglandin synthetase inhibitors** - indomethacin
- **Nitric oxide donors** - glyceryltrinitrate
- **Oxytocin receptor antagonists** - atosiban, barusiban
- **Magnesium sulfate**

Ethyl alcohol was frequently prescribed as a tocolytic in the mid-20th century, but later double-blind studies showed that it was not effective.
Challenges that clinicians are facing

Preterm birth remains a major cause of neonatal mortality and long term disability and the biggest challenge for clinicians is to identify women at risk so that unnecessary treatment is not given to women who do not require it. Moreover being able to identify women at high risk of preterm labor will allow the design of clinical studies to target women who are the most likely to benefit from any intervention. The major stumbling block for progress in the management of preterm labor is the lack of knowledge of the mechanism of parturition. We need to identify the endocrine and biochemical processes that explain why women go into labor. Only then will it possible to know whether preterm labor is an acceleration of the same mechanism that operates at term or whether it is precipitated by other physiopathological shortcuts. This knowledge will also help in the management of dysfunctional labor and improve the success rate of induction of labor. For neonatologists very early and extremely early preterm birth will continue to pose very difficult challenges. Further work is required to assess the long term impact of the sensorineural deficits and behavioral alterations associated with preterm birth.

The consensus views of experts in preterm birth can be summarized as follows [225]:

- The elucidation of the physiological pathways of normal labor at term is essential, as a prerequisite for understanding preterm labor.
  This should include further studies on the physiology of the human myometrium and of cervical ripening.

- To this end more interdisciplinary research is needed including high quality clinical studies of adequate power to address neonatal and infant outcome.

- More clinical studies are needed to:
  – determine the risk and benefits of repeated administration of corticosteroids
  – determine the optimal timing for induction of labor in women with PPROM

- The benefits/risks of tocolysis, progesterone or any other treatments should be investigated in randomized placebo-controlled trials.

- Pharmacological targets that are selective to the uterus should be identified to increase effectiveness and minimize side effects.

- The significance of abnormal intraterine bacterial colonization in spontaneous preterm labor requires further investigation.

- The role of intraterine immune cells and inflammatory mediators in spontaneous labor needs to be defined.

- The management of PPROM will benefit from improved understanding of the repair process in the fetal membranes.
Concluding remarks

The last trimester of pregnancy is necessary for the maturation of the fetal lungs and other organs in preparation for extrauterine life. If this process is interrupted by an early delivery the chances of survival of the newborn are severely decreased [226]. Preterm birth affects both rich and poor countries but the former often have the advantage of better neonatal care. Despite considerable improvements in obstetrics and neonatology the perinatal mortality rates in many countries have remained relatively constant for decades. Even in hospitals where survival rates have improved, there is a wide range of both short-term and long-term morbidity and handicap in the surviving infants, particularly in the very preterm and extremely preterm groups. The high rate of neurosensory disabilities in these infants poses a severe and lasting challenge to society [227].

The quality of research into human parturition and preterm labor is high; however it reflects fragmented efforts from groups that work in relative isolation. There is a need for concerted research efforts from different laboratories to make substantial contributions towards solving the problem of preterm labor. This will require traditional physiological and biochemical studies as well as modern genomic and proteomic approaches and new imaging techniques, electromyography, bioengineering and nanotechnology. Moreover the development of any new biomarkers, diagnostic methods and uterine selective drugs must be validated with appropriately designed clinical trials of sufficient power to reach robust conclusions.[228, 229, 230]
Global efforts in preventing preterm birth

Examples of efforts made to address the growing problem of PTB

The March of Dimes
(www.marchofdimes.com) USA (Founded 1938)

March of Dimes is an organization with a mission to improve the health of babies by preventing birth defects, premature birth, and infant mortality. The March of Dimes carries out this mission through programs of research, community services, education and advocacy to save babies’ lives.

The March of Dimes Prematurity Campaign is a multimillion-dollar research, awareness and education effort that helps families to have healthier babies (launched on January 30, 2003).

Campaign Goals:

• Raising awareness of prematurity
• Reducing the rate of premature births

March of Dimes has published an evidence-based Preterm Labor Assessment Toolkit. The objective of the toolkit is to standardize the assessment and diagnosis of preterm labor among health care professionals.

EAPM, European Association of Perinatal Medicine
(www.europerinatal.com/new_site) Europe (Founded in 1968)

The purpose of the Association is to bring together groups and individuals in a European organization in order to promote the science of perinatal medicine for the benefit of a high level of physical and mental health for women, mothers and their children in Europe.

Current study group:
European Association of Perinatal Medicine-Study Group on “Preterm Birth”

SMFM, Society for Materna-Fetal Medicine
(www.smfm.org) USA (Founded in 1977)

The Society for Maternal-Fetal Medicine is the membership organization for obstetricians/gynecologists who have additional formal education and training in Maternal-Fetal medicine. The Society hosts an annual scientific meeting. The Society is also an advocate for improving public policy and expanding research funding and opportunities in the area maternal-fetal medicine.

Specially educated Maternal-Fetal Medicine sub-specialists provide care or consultation for both mother and fetus in a complicated pregnancy. Examples of types of patients seen by Maternal-Fetal Medicine sub-specialists:

• Twins, triplets or more
• Recurrent pre-term labor and delivery
• Premature rupture of membranes
• Recurrent pregnancy loss
ACOG, American College of Obstetrics and Gynecology
(www.acog.org) USA (Founded in 1951)

The American College of Obstetricians and Gynecologists is a professional association of medical doctors specializing in obstetrics and gynecology in the United States.

ACOG pursues its PTB mission through:
- Education
- Research
- Practice
- Guidelines and recommendation

NANE, North Atlantic Neuro-Epidemiology Alliances
(www.nanea.dk) Denmark and USA

NANE is a scientific collaboration between two organizations: University of Aarhus, Denmark (AU), and Centers for Disease Control and Prevention, Atlanta, USA (CDC).

NANE's main areas of research presently include:
- cerebral palsy
- preterm delivery
- lifestyle during pregnancy
- autism

PREBIC Preterm Birth International Collaborative
(www.prebic.net) International (Founded in 2004)

The International PREterm Birth Collaborative (PREBIC) was initiated on June 7th 2004 during a workshop on Biomarkers and Preterm Birth in Denmark.

The purpose of the collaborative is to support and enhance international networking among researchers in preterm birth and the establishment of multinational research projects on preterm birth.

PGP, Preterm birth Genome Project
International (Founded in 2007)

PGP consortium includes investigators from 4 continents. This community of researchers collaborates to identify PTB susceptibility genes. The PGP Management Committee consists of members chosen from the PGP and PREBIC. A WHO representative serves as Chair of the Management Committee.

The goal of the collaboration is to identify genes that affect susceptibility to preterm birth (PTB) and other adverse pregnancy outcomes associated with preterm birth. This objective will be expedited by combining the resources of multiple research groups from around the world.
SAFE, The Special Non-Invasive Advances in Fetal and Neonatal Evaluation Network

(www.safenoe.org) Europe (Founded in 2004)

The Special Non-Invasive Advances in Fetal and Neonatal Evaluation Network is a European consortium aiming at developing of noninvasive diagnosing methods. The SAFE Network is set to run for a period of 5 years. It is sponsored under the EU Framework 6 program and has 49 partners from 19 countries.

European Preterm labour Group, was created following scientific meetings sponsored by SAFE, to cement collaboration and publicize the need to invest research funds into a better understanding of parturition and preterm labor.

Action Medical Research

(www.action.org.uk) UK (Founded 2003)

An independent national charity relying on voluntary support. Action Medical Research currently fund 68 top-quality research projects, representing a funding commitment of £7 million.

Touching Tiny Lives is Action Medical Research’s campaign highlighting the urgent need for more research to help sick and vulnerable babies. The aim is to raise £3 million for vital new research to help prevent premature birth and life-threatening pregnancy complications.

Tommy’s the Baby Charity

(www.tommys.org) UK (Founded 1992)

UK’s leading baby charity committed to funding medical research and providing pregnancy information.

Tommy’s exists to save babies’ lives through funding research into and providing information on the causes and prevention of miscarriage, premature birth and stillbirth. The goal is to halve the number of babies who die during pregnancy or birth by 2030.

CPN, BILBO, Canadian Neonatal Network, Birth before 29 weeks project

(www.cpn-rpc.org) Canada (Founded 2003)

CPN is made up of Canadian researchers who will collaborate on research issues relating to perinatal care.

BILBO will be building a standardized national database of pregnancies at high risk of very preterm birth at 22 to 28+ weeks’ gestation. These networks provide an opportunity for researchers to participate in collaborative projects on a national scale.

GAPPS, The Global Alliance for the Prevention of Prematurity and Stillbirth

(gappssseattle.org) USA

Based at Seattle Children’s Hospital. Director Craig Rubens, MD, PhD.

GAPPS brings together an international team of maternal and child health researchers to address the worldwide problems of preterm births and stillbirth.
Glossary and abbreviations

A

Adrenocorticotropic hormone (ACTH or corticotropin)
Polypeptide hormone produced and secreted by the pituitary gland. It is an important player in the hypothalamic-pituitary-adrenal axis.

Alloantigen
An antigen existing in alternative (allelic) forms in a species, thus inducing an immune response when one form is transferred to members of the species who lack it.

American College of Obstetricians and Gynecologist (ACOG)
A professional association of medical doctors specializing in obstetrics and gynecology in the United States.

Amnioinfusion
the instillation of fluid into the pregnant uterine cavity before delivery.

Amniotic fluid
A clear, slightly yellowish liquid that surrounds the unborn baby (fetus) during pregnancy. It is contained in the amniotic sac.

Antepartum hemorrhage
Bleeding from the vagina during pregnancy.

Antigen
is any substance that causes the immune system to produce antibodies against it. An antigen may be a foreign substance from the environment such as chemicals, bacteria, viruses, or pollen. An antigen may also be formed within the body, as with bacterial toxins or tissue cells.

Apnea
A technical term for suspension of external breathing. During apnea there is no movement of the muscles of respiration and the volume of the lungs initially remains unchanged.

Appendicitis
A condition characterized by inflammation of the appendix. While mild cases may resolve without treatment, most require removal of the inflamed appendix.

Assisted reproductive technologies (ART)
All fertility treatments in which both eggs and sperm are handled.

B

Bacteremia
Presence of bacteria in blood

Bacterial vaginosis (BV)
A mainly asymptomatic syndrome in which the normal vaginal lactobacilli are replaced by a mixed flora with high concentrations of anaerobic bacteria.

Bacteriuria
Presence of bacteria in urine.

Bishop score
is a pre-labor scoring system to assist in predicting whether induction of labor will be required. Also used to estimate the risk of preterm birth.

Braxton Hicks contractions
Sporadic uterine contractions, also known as false labor or practice contractions.

C

Cerebral palsy (CP)
Any one of a number of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination but do not become worse with time.

Cervical cerclage
A surgical procedure, in which the cervix is sewn closed during pregnancy. It is used for the treatment of cervical incompetence, a condition where the cervix has become slightly open and there is a risk of miscarriage or preterm birth because it may not remain closed throughout pregnancy.

Cervical insufficiency/incompetence
Weakened cervix that predisposes a woman to mid-term miscarriage or early (premature) delivery because it opens too early.
Cervical length (CL)
Length of the cervix is a measure inversely related to the risk of preterm labor. It is assessed manually or, more reliably with transvaginal ultrasonography.

Cervix
The lower, narrow end of the uterus where it joins with the top end of the vagina.

Cervical ripening
A complex process that results in physical softening and distensibility of the cervix, ultimately leading to partial cervical effacement and dilatation.

Cesarean section= (C-section)
A surgery to deliver a baby. The baby is taken out through the mother’s abdomen. Most C-sections are done when unexpected problems occur during delivery.

Chorioamnionitis
An infection of the membranes (placental tissues) and amniotic fluid.

Chorion
The outermost of the two fetal membranes – the amnion is the innermost – which together surround the embryo.

Chlamydia
A common sexually transmitted disease (STD) caused by the bacterium, Chlamydia trachomatis.

Coagulopathy
A medical term for a defect in the body’s mechanism for blood clotting.

Corticosteroid
Hormones given to mature fetal lungs, for arthritis, or other medical conditions.

Complex disorder
Disorder caused by the interaction of multiple genes, or by a combination of genetic and environmental risk factors.

Corticotropin-releasing hormone (CRH)
A polypeptide hormone and neurotransmitter involved in the stress response.

Cortisol
A corticosteroid hormone produced by the adrenal cortex (in the adrenal gland). It is a vital hormone that is often referred to as the “stress hormone” as it is involved in the response to stress.

Cytokines
A group of proteins and peptides that are used in organisms as signaling compounds. These chemical signals are similar to hormones and neurotransmitters and are used to allow one cell to communicate with another. Cytokines have been variously called lymphokines, interleukins and chemokines, based on their presumed function, cell of secretion or target of action.

Decidua
The term for the uterine lining (endometrium) during a pregnancy, which forms the maternal part of the placenta.

Demographic
Demographics refers to selected population. Commonly-used demographics include race, age, income, disabilities, mobility, educational attainment, and employment status.

Digital examination
An examination with fingers (v. lat. digitus, “finger”).

Endotoxins
Toxic, natural compounds found inside pathogens such as bacteria. Endotoxin is not secreted by live bacteria, but is a structural component in the bacteria, which is released mainly when bacteria are lysed.

Endocannabinoids
Substances produced within the body which activate cannabinoid receptors.

Estriol (E3)
One of the three main estrogens produced by the human body. It is only produced in significant amounts during pregnancy as it is made by the placenta.
Etiology
The study of the causes of a disease.

Extremely low birth weight (ELBW)
An infant that weighs less than 1000 g at delivery, regardless of the gestational age at birth.

F

Fetus
A baby growing in the woman’s uterus.

Fetal fibronectin (fFN)
An extracellular glycoprotein that is thought to act as the adhesive substance, or “tissue glue” between the membranes and the uterine wall.

Fetal membranes
Thin layers of tissue which surround the embryo or fetus and provide for its nutrition, respiration, excretion and protection; they are the yolk sac, allantois, amnion, and chorion.

Fetal inflammatory response syndrome (FIRS)
A condition characterized by systemic inflammation of the fetus and an elevation of fetal plasma interleukin-6. FIRS is associated with the impending onset of preterm birth.

Folate
A form of a water-soluble B vitamin. Folate occurs naturally in food (e.g. leafy vegetables such as spinach, dried beans and peas). Folate is necessary for the production and maintenance of new cells. This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to make DNA and RNA. It also helps prevent changes to DNA that may lead to cancer.

G

Gap junction
Intercellular channels that permit the free passage between the cells of ions and small molecules. As the time of birth approaches, gap junctions between the smooth muscle cells of the uterus enable coordinated, powerful contractions to begin.

Genetic polymorphism
A difference in DNA sequence among individuals, groups, or populations.

Granulocyte colony-stimulating factor (G-CSF)
A blood growth factor that stimulates the bone marrow to produce more infection-fighting white blood cells called neutrophils.

H

Home uterine monitoring (HUAM)
An at-home device used to monitor a pregnant woman’s uterine contractions to detect premature labor.

Hyperemesis gravidarum
A rare disorder characterized by severe and persistent nausea and vomiting during pregnancy that may necessitate hospitalization.

Hypothalamic-Pituitary-Adrenal (HPA) axis
The body’s neuroendocrine system that involves the hypothalamus, pituitary, and adrenal glands. This complex communication system is responsible for effectively handling stress and regulates various body processes including digestion, the immune system, mood and sexuality, and energy usage by regulating the production of cortisol, neurotransmitters and key hormones.

I

Iatrogenic = “intentional”
In a preterm birth context it means that the physician decides that the baby needs to be delivered preterm, due to serious maternal or fetal complications.

Interleukins (IL)
The cytokines that act specifically as mediators between leucocytes.

Intrauterine growth restriction (IUGR)
A failure of normal fetal growth. It is caused by multiple adverse effects on the fetus that inhibit normal growth potential.

Intraventricular hemorrhage (IVH)
Bleeding inside or around the ventricles, the spaces in the brain containing the cerebral spinal fluid.

Intraventricular hemorrhage is most common in premature babies, especially very low birth weight babies. Bleeding in the brain can put pressure on the nerve cells and damage them. Severe damage to cells can lead to brain injury.
L

Low-birth weight (LBW)
An infant that weighs less than 2,500 grams at delivery, regardless of the gestational age at birth.

M

Matrix metalloproteinases (MMPs)
A member of a group of enzymes that can break down proteins, such as collagen, that are normally found in the spaces between cells in tissues (i.e., extracellular matrix proteins). Because these enzymes need zinc or calcium atoms to work properly, they are called metalloproteinases. Matrix metalloproteinases are involved in wound healing, angiogenesis, and tumor cell metastasis.

Mucinase
An enzyme that acts upon mucin (glycoproteins found in the secretions of mucous membranes).

Myometrium
The middle layer of the uterine wall consisting of smooth muscle cells and supporting stromal and vascular tissue.

N

Necrotizing enterocolitis (NEC)
A medical condition primarily seen in premature infants, where portions of the bowel undergo necrosis (tissue death).

Negative predictive value (NPV)
The probability that a person does not have the target disorder when a negative test result is observed.

O

Oligohydramnios
Too little fluid in the uterine cavity.

Oxytocin
A hormone that also acts as a neurotransmitter in the brain. In females, it is released in large amounts after distension of the cervix and vagina during labor, and after stimulation of the nipples, facilitating birth and breastfeeding, respectively.

P

Patent ductus arteriosus (PDA)
A congenital heart defect wherein a child’s ductus arteriosus fails to close after birth.

Periventricular leukomalacia (PVL)
A condition characterized by the death of the white matter near the cerebral ventricles due to softening of the brain tissue. It can affect fetuses or newborns; premature babies are at the greatest risk of the disorder.

Periodontal disease (PD)
= “gum disease”
A chronic bacterial infection that affects the gums and bone supporting the teeth. It has been found to be associated with preterm birth.

Phospholipase
An enzyme that catalyzes the hydrolysis of a phospholipid.

Phosphorylated insulin like growth factor binding protein-1 (phIGFBP-1)
A carrier protein for insulin-like growth factor 1. During pregnancy, IGFs and their binding proteins (IGFBPs) are important for the growth of fetal and maternal tissues. The highly phosphorylated isoform (phIGFBP-1) is produced by the decidua. It is an indicator of tissue damage at the choriodecidual interface in pregnant women and a marker of increased risk of infectious complications such as bacterial vaginosis.

Placental abruption
Separation of the placenta from the wall of the uterus.

Pneumonia
Inflammation of the lungs.

Polyhydramnios
The medical condition of too much amniotic fluid in the amniotic sac.

Positive predictive value (PPV)
The probability that a person has the target disorder when a positive test result is observed.

Pre-eclampsia (PE)
A disorder that occurs during pregnancy. Characterized by increased blood pressure and protein in urine.
Preterm premature rupture of membranes (PPROM)
Rupture of fetal membranes prior to 37 weeks gestation. Very often leads to preterm birth.

Preterm birth (PTB)
Delivery that occurs before 37 completed weeks of pregnancy.

Preterm labor (PTL)
Labor (regular contractions and cervical ripening) starting before 37 complete weeks of gestation, with intact fetal membranes.

Progesterone
A female hormone that is produced in the ovaries and makes the lining of the uterus grow. When the level of progesterone decreases, menstruation occurs.

Progestin
A natural or synthetic substance that mimics some or all of the actions of progesterone.

Proinflammatory cytokines
Cytokines that are involved in the amplification of inflammatory reactions. These include IL-1, IL-6, TNF-α, and TGF-β.

Prostaglandin
One of a number of hormone-like substances that participate in a wide range of body functions such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, control of blood pressure, and modulation of inflammation. Prostaglandins are derived from a chemical called arachidonic acid.

Protease
An enzyme that digests proteins.

Pyelonephritis
An ascending urinary tract infection that has reached the pyelum (pelvis) of the kidney.

Respiratory distress syndrome (RDS)
A syndrome caused in premature infants by developmental insufficiency of surfactant production and structural immaturity in the lungs.

Retinopathy
A general term that refers to some form of non-inflammatory damage to the retina of the eye. Prematurity is one of the main causes of retinopathy.

S

Sepsis
An infection of the blood

Single nucleotide polymorphism (SNP) (pronounced snip)
A DNA sequence variation occurring when a single nucleotide - A, T, C, or G - in the genome differs between members of a species or between paired chromosomes in an individual.

Small for gestational age, SGA
An infant whose weight is lower than the population norms. It is defined as weight below the 10th percentile for gestational age.

Spiral artery
The corkscrew-like arteries in premenstrual or gestational endometrium.

Systemic infections
Invasion of the bloodstream by virulent microorganisms (such as bacteria, viruses, or fungi) from a focus of infection that is accompanied by acute systemic illness.

Thrombin
Is an enzyme that presides over the conversion of fibrinogen to fibrin. Thrombin is thus a key clot promoter.

Tocolytic
Medications used to suppress or slow preterm premature labor.

Transient dystonia
An abnormality of muscle tone often demonstrated in infants under one year of age who were born preterm. It may mimic the condition of cerebral palsy.

Transvaginal ultrasonography (TVU)
Ultrasonography in which a probe is inserted into the vagina.

U

Urocortin
With urocortin II a member of the corticotropin-releasing hormone (CRH) family of neuropeptides that function to regulate stress responses.
Uterotonin
Cause uterine contractions (e.g. oxytocin and prostaglandins).

Ultrasonography (or sonography)
A test in which sound waves are used to examine internal structures. During pregnancy, it can be used to examine the fetus. Transvaginal ultrasonography is used to measure cervical length.

Ventouse
A vacuum device used to assist the delivery of a baby when labor has not progressed adequately.

Very low birth weight (VLBW)
An infant that weighs less than 1500 g at delivery, regardless of the gestational age at birth.
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