Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis

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INTRODUCTION

Preterm birth (PTB) refers to a delivery that occurs between 20 and 37 weeks of gestation (table 1). Seventy to 80 percent of PTBs are spontaneous: due to preterm labor (40 to 50 percent) or preterm prelabor rupture of membranes (20 to 30 percent); rarely, cervical insufficiency results in spontaneous PTB (sPTB). The remaining 20 to 30 percent of PTBs are iatrogenic: due to maternal or fetal issues that jeopardize the health of the mother or fetus (eg, preeclampsia, placenta previa, abruptio placentae, fetal growth restriction, multiple gestation). Complications of pregnancy can lead to both sPTB and provider-initiated PTBs.

PTB is relatively common, occurring in 5 to 18 percent of births worldwide (see "Incidence and mortality of the preterm infant", section on "Incidence"). There are many risk factors for PTB (table 2) and many pathways from these risk factors to the terminal cascade of events resulting in labor. Preterm labor likely occurs when local uterine factors prematurely stimulate this cascade or suppressive factors that inhibit the cascade and maintain uterine quiescence are withdrawn prematurely. (See "Spontaneous preterm birth: Pathogenesis").

Ideally, identification of modifiable and nonmodifiable risk factors for PTB before conception or early in pregnancy will lead to interventions that help prevent this complication. However, few interventions have been proven to prolong pregnancy in women at risk. This goal has been elusive for several reasons: two-thirds of PTBs occur among women with no risk factors, causality has been difficult to prove (eg, a cofactor may be required thus complicating the chain of causality), and no adequate animal model exists for study of sPTB.

Risk factors for PTB and potential interventions to mitigate risk, when possible, will be reviewed here. Pathogenesis of PTB and diagnosis and treatment of preterm labor are
discussed separately:

- (See "Spontaneous preterm birth: Pathogenesis".)
- (See "Inhibition of acute preterm labor".)
- (See "Preterm labor: Clinical findings, diagnostic evaluation, and initial treatment".)

REPRODUCTIVE HISTORY

**History of spontaneous preterm birth** — A history of sPTB is the major risk factor for recurrence, and recurrences often occur at the same gestational age [1-3]. Women at highest risk are those with:

- No term pregnancy between the previous sPTB and the current pregnancy
- A history of multiple sPTBs

In large series, the frequency of recurrent sPTB was 15 to 30 percent after one sPTB and even higher after two sPTBs [4-8]. The odds of recurrent sPTB in three high-income countries (New Zealand, Sweden, Slovenia) ranged from 4.5 to 7.1 in one study [9]. Term births decrease the risk of sPTB in subsequent pregnancies (table 3 and table 4).

The risk of recurrent early sPTB is of particular concern given its high morbidity and mortality. In a large prospective series, approximately 5 percent of women who had an early sPTB at 23 to 27 weeks in their prior pregnancy delivered at <28 weeks in their subsequent pregnancy [4]. By comparison, if there was no previous history of sPTB, then the risk of sPTB <28 weeks was only 0.2 percent.

Other characteristics of the prior sPTB may also predict recurrence risk. In a small retrospective cohort study, women who presented with painless advanced cervical dilation were significantly more likely to have recurrent sPTB than women with a history of preterm prelabor rupture of membranes or preterm labor (55 versus 27 versus 32 percent, respectively) [10]. The increased risk remained after adjustment for gestational age of the last PTB.

Women who were born preterm are at modestly increased risk of having a sPTB compared with women who were born at term. (See 'Genetic factors' below.)

A prior sPTB of twins is associated with an increased risk of sPTB in a subsequent singleton pregnancy. In a meta-analysis assessing the risk of PTB in singleton pregnancies after a previous twin birth, compared with a previous twin term birth, the odds of subsequent preterm singleton birth (all causes) were 2.13 (95% CI 1.21-3.74) if the previous twins were born at 34+0 to 36+6 weeks of gestation, 5.18 (95% CI 2.78-9.64) if they were born at 30+0 to 33+6 weeks, and 9.73 (95% CI 4.99-18.98) if they were born at <30+0 weeks [11]. The odds
ratios (ORs) were similar (2.71, 5.74, and 6.54, respectively) when only twin sPTBs were considered.

The overall risk of sPTB in twin pregnancy is significantly higher in multiparous women whose previous singleton pregnancy was a sPTB: 67.3 percent versus 20.9 percent if the previous singleton delivery was at term (OR 7.8, 95% CI 5.5-11.2) [12].

**Intervention**

- **Progesterone** supplementation appears to reduce the risk of PTB by approximately 20 percent in women with a singleton pregnancy and a history of sPTB or a short cervix. A review of evidence and treatment approaches is available separately. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth").

- In women with a history of PTB in whom the diagnosis of cervical insufficiency is uncertain, sonographic evidence of a short cervix in the midtrimester can identify those who may benefit from placement of a cerclage (ultrasound-induced cerclage). Women with multiple second-trimester pregnancy losses/PTBs associated with painless cervical dilation may benefit from early placement of a cerclage based on this history alone (history-indicated cerclage) (table 5). A review of screening and treatment approaches and supporting evidence is available separately.
  - (See "Short cervix before 24 weeks: Screening and management in singleton pregnancies", section on ‘Parous women with a prior spontaneous preterm singleton birth’.)
  - (See "Cervical insufficiency".)

- A short interpregnancy interval has been associated with an increased risk of PTB. The March of Dimes encourages women to space pregnancies at least 18 months apart. (See 'Short interpregnancy interval' below.)

- Although an increase in uterine activity is a prerequisite for labor, randomized trials and a meta-analysis have shown that self-measurement of the frequency of uterine contractions by self-palpation/detection of signs of labor or through use of a home uterine activity monitor does **not** lead to a reduction in the rate of PTB [13,14]. Moreover, such an approach increases the frequency of unscheduled antenatal visits. The American College of Obstetricians and Gynecologists recommends not using home uterine activity monitoring as a screening strategy for prediction or prevention of PTB [15].

- Prophylactic tocolytic therapy for prevention of PTB in high-risk asymptomatic women is **not** effective, although few randomized trials have been conducted [16,17]. (See
History of indicated preterm birth — A large retrospective cohort study assessed the risk of recurrent PTB by the type of PTB in the previous pregnancy [7]. The rate of recurrent PTB was 23 percent for women with a prior indicated PTB and 31.6 percent for women with a prior sPTB. Women with a prior indicated PTB were at particularly high risk for recurrent indicated PTB (relative risk [RR] 9.10, 95% CI 4.68-17.71) but also at increased risk of sPTB (RR 2.70, 95% CI 2.00-3.65). Women with a prior sPTB were at five- to sixfold increased risk for recurrent sPTB, but also appeared to be at slightly increased risk for indicated PTB (RR 1.61, 95% CI 0.98-2.67).

Intervention

- Interventions to reduce the risk for recurrent indicated PTB depend on the indication for PTB. For example, administration of low-dose aspirin to women with a history of early delivery because of preeclampsia with severe features can reduce their risk for recurrent preeclampsia and PTB. (See "Preeclampsia: Prevention", section on 'Low-dose aspirin'.)

History of abortion — In a systematic review of pregnancy outcome after uterine evacuation including over one million women (31 studies involving termination of pregnancy, five studies involving spontaneous abortion), women with a history of surgical uterine evacuation had a small but statistically significant increase in risk for PTB in a subsequent pregnancy compared with controls [18]. Women who underwent medical termination of pregnancy had a similar future risk of PTB as women with no history of pregnancy termination.

Although surgical uterine evacuation appeared to be a risk factor for subsequent PTB, observational studies are flawed because they are subject to recall bias and inadequate adjustment of many of the other risk factors for adverse pregnancy outcome. (See "Overview of pregnancy termination", section on 'Future pregnancies'.)

GENETIC FACTORS

Genetic polymorphisms appear to contribute to length of gestation and a woman's likelihood of sPTB. In a genomewide association study of a large cohort of women of European ancestry, maternal variants at the EBF1, EEFSEC, AGTR2, WNT4, ADCY5, and RAP2C loci were associated with gestational duration and maternal variants at the EBF1, EEFSEC, and AGTR2 loci were associated with PTB; however, birth outcomes were self-reported [19]. Although PTB susceptibility genes have been identified, epigenetic and gene-environmental factors probably play a more important role in PTB than the maternal genotype.
PTBs are more prevalent in some family pedigrees and racial groups, in women who were born preterm themselves, and in women with a first-degree female relative who had a PTB [20,21]. In addition, concordance for timing of parturition is higher in women who are monozygotic twins than in those who are dizygotic twins [3,22-32].

The paternal genotype does not have a significant effect on PTB. (See 'Paternal risk factors' below.)

NON-HISPANIC BLACK RACE

In the United States, non-Hispanic Black women consistently have a higher rate of PTB than non-Hispanic White women [33]. In a meta-analysis of eight English-language studies including over 26 million singleton births, the odds of PTB were lowest in couples in which both parents were White and progressively increased with Black parentage: White mother/White father (odds ratio [OR] 1.0), White mother/Black father (OR 1.17), Black mother/White father (OR 1.37), Black mother/Black father (OR 1.78) [34]. This may be related to both genetic and environmental factors (eg, social, educational, occupational, economic). A discrepancy between Black and White populations in the risk of recurrent PTB has also been observed. In Black and White women whose first delivery was at 20 to 31 weeks of gestation, the frequency of a second delivery at the same gestational age range was 13.4 and 8.2 percent, respectively, in one study [4,35]. For the gestational age range 32 to 36 weeks, the frequency of a second delivery at the same gestational age was 3.8 and 1.9 percent, respectively.

Differences in epidemiologic and environmental risk factors account for some of the increased risk in PTB, but polymorphisms in genes for regulation of innate immunity also appear to play a role [36-39]. Women's race/ethnicity seems to influence their microbiome and the impact of vaginal bacteria on PTB [40-43]. One mechanism may involve an enhanced proinflammatory response to normal or altered vaginal microflora, leading to preterm labor or preterm prelabor rupture of membranes (PPROM) [44]. Alternatively, immune hyporesponsiveness may create a permissive environment for ascending infection and its sequelae (premature labor, PPROM) [45,46]. (See "An overview of the innate immune system".)

AGE

The rate of PTB is higher at the extremes of maternal age [47-49]. Physiologic immaturity and socioeconomic factors may increase risk for adolescent mothers; a higher prevalence of preexisting chronic disease and obesity may increase risk for older mothers. Both groups
have high rates of unintended pregnancy; prevention of these pregnancies may reduce PTB [50].

**CERVICAL SURGERY**

Cold knife conization and loop electrosurgical excision procedures for treatment of cervical intraepithelial neoplasia have been associated with increased risks for late miscarriage and PTB. Possible mechanisms include loss of tensile strength from loss of cervical stroma, increased susceptibility for infection from loss of cervical glands, and loss of cervical plasticity from cervical scarring. (See "Reproductive effects of cervical excisional and ablative procedures".)

**Intervention**

- Women undergoing treatment of cervical intraepithelial neoplasia should have the procedure that best diagnoses or prevents cervical cancer and also incurs the lowest risk of reproductive effects.

  Although women who have undergone cervical surgery may develop cervical insufficiency, the pregnancy course and outcome need to be evaluated before making this diagnosis. We perform a single transvaginal ultrasound measurement of cervical length measurement at 18 to 24 weeks in all women and treat those with a short cervix (≤25 mm) and no prior PTB with vaginal progesterone supplementation. (See "Cervical insufficiency", section on 'Women with no prior second-trimester pregnancy loss/extremely preterm birth, but risk factors for cervical insufficiency'.)

**UTERINE MALFORMATIONS**

**Congenital** — In women with congenital uterine malformations, the magnitude of risk for PTB depends upon the specific abnormality [51-53]. (See "Congenital uterine anomalies: Clinical manifestations and diagnosis".)

**Intervention**

- Surgical correction of the abnormality may reduce the risk for PTB. (See "Congenital uterine anomalies: Surgical repair".)

**Acquired** — Women with fibroids may be at slightly increased risk for pregnancy loss and PTB. A large fibroid (ie, ≥5 to 6 cm) or multiple fibroids appear to be the most important risk factors for PTB; a submucosal location is the most important risk factor for pregnancy loss.
Intervention

- Myomectomy before pregnancy may be indicated in women with pregnancy loss or early PTB. Every effort should be made to avoid surgical removal of fibroids during pregnancy because of the risk for significant morbidity (hemorrhage). (See "Uterine fibroids (leiomyomas): Issues in pregnancy".)

**CHRONIC MEDICAL DISORDERS**

Chronic maternal medical disorders can be associated with maternal or fetal complications necessitating medically indicated PTB as well as an increased risk for sPTB. Examples include women with hypertension, renal insufficiency, type 1 diabetes mellitus, some autoimmune diseases, and nonphysiologic anemia.

Both depression and exposure to selective serotonin reuptake inhibitors have been associated with an increased risk of PTB. (See "Antenatal depression: Pregnancy and neonatal outcomes", section on 'Preterm birth' and "Antenatal use of antidepressants and risk of teratogenicity and adverse pregnancy outcomes: Selective serotonin reuptake inhibitors (SSRIs)", section on 'Preterm birth'.)

**Intervention**

- Preconception identification and optimization of chronic medical diseases, such as diabetes and hypertension, can improve maternal health and pregnancy outcome. (See "The preconception office visit".)

- Optimization of depression symptoms is also desirable. (See "Unipolar major depression in pregnant women: General principles of treatment".)

**PREVIOUS INFANT WITH SUDDEN INFANT DEATH SYNDROME**

A history of delivery of an infant who subsequently died from sudden infant death syndrome appears to be a risk factor for PTB in the following pregnancy [54]. (See "Sudden infant death syndrome: Risk factors and risk reduction strategies".)

**ASSISTED REPRODUCTION**
Pregnancies conceived by assisted reproduction are at higher risk for sPTB, even in the absence of multifetal gestation. The increased risk may be related to baseline maternal factors related to subfertility and/or factors related to assisted reproduction procedures. (See "Pregnancy outcome after assisted reproductive technology", section on 'Preterm birth, low birth weight, and small for gestational age'.)

MULTIFETAL GESTATION

Multifetal gestation accounts for only 2 to 3 percent of all births but 17 percent of births before 37 weeks of gestation and 23 percent of births before 32 weeks. The widespread availability of assisted reproductive technology has resulted in a large increase in the incidence of multiple gestation; this increase, in turn, has led to an increase in sPTB and indicated PTB [55].

The mechanism for sPTB in multifetal gestations, and particularly higher-order multifetal gestations, may be related to sequelae of increased uterine distention (see "Spontaneous preterm birth: Pathogenesis", section on '#4 Pathologic uterine distention'). The endocrine environment produced by superovulation or the multiple pregnancy may also play a role. As an example, multifetal gestations produce increased amounts of estrogen, progesterone, and sex steroids compared with singleton pregnancies [56,57]. Increased steroid production may be a factor in initiation of labor (see "Physiology of parturition at term"). Higher circulating levels of relaxin associated with super-ovulation may cause cervical insufficiency with subsequent sPTB [58].

Intervention

- Prevention and reduction of multifetal gestations, particularly high-order multifetal gestations, appear to improve neonatal outcome. (See "Strategies to control the rate of high order multiple gestation" and "Multifetal pregnancy reduction and selective termination".)

- In unselected twin pregnancies, progesterone supplementation, use of a pessary, cerclage, and bed rest/reduction of physical activity do not prolong gestation. In women with a twin pregnancy and a prior singleton sPTB or a short cervix, the use of supplemental progesterone or a pessary is controversial and reviewed separately. (See "Twin pregnancy: Management of pregnancy complications", section on 'Overview' and "Twin pregnancy: Management of pregnancy complications", section on 'Approach to patients with a short cervix' and "Progesterone supplementation to reduce the risk of spontaneous preterm birth".)
VAGINAL BLEEDING IN EARLY PREGNANCY

Early pregnancy bleeding is often due to decidual hemorrhage and associated with an increased risk for both subsequent sPTB and indicated PTB. In a large study based on registry data, pregnancies with first-trimester bleeding were at increased risk for preterm prelabor rupture of membranes (PPROM; odds ratio [OR] 1.18, 95% CI 1.01-1.37), placental abruption (OR 1.48, 95% CI 1.30-1.68), and severe preeclampsia (OR 1.25, 95% CI 1.09-1.43) [59]. In this and other studies, the association was stronger for PTB before 34 weeks than late PTB [59,60]. Women with persistent vaginal bleeding and bleeding in the second trimester are at higher risk of these complications than those with an isolated first-trimester event.

Decidual hemorrhage results in release of tissue factor, which can trigger local thrombin formation. Decidual thrombin production has been associated with increased expression of soluble fms-like tyrosine kinase-1 (sFlt-1) and monocyte-recruiting chemokines, factors also associated with subsequent indicated PTB due to preeclampsia, abruption, or fetal growth restriction as well as subsequent sPTB [61]. Later in pregnancy, decidual cell-derived thrombin can inhibit decidual cell progesterone receptor expression, possibly resulting in PTB related to abruption or PPROM [62-64]. (See "Spontaneous preterm birth: Pathogenesis", section on '#3 Decidual hemorrhage'.)

Intervention

- Women with a history of PTB may be treated with progesterone to prevent recurrence in a subsequent pregnancy. Those who have vaginal bleeding/abruption in the subsequent pregnancy still appear to respond to hydroxyprogesterone caproate prophylaxis in that pregnancy [65]. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth".)

SHORT CERVIX

There is an inverse relationship between cervical length measured by transvaginal ultrasound at 16 to 28 weeks of gestation and gestational age at delivery (table 6). A high Bishop score on digital examination is also associated with increased odds of PTB [66]. (See "Short cervix before 24 weeks: Screening and management in singleton pregnancies".)

Intervention

- For women with singleton pregnancies and no history of prior PTB, we suggest screening for a short cervix (≤25 mm) with a single examination at 18 to 24 weeks, which can be performed in conjunction with the fetal anatomic survey ultrasound examination.
**Bed rest is not helpful** — Bed rest improves uteroplacental blood flow and can lead to a slight increase in birth weight, but there is no evidence that it decreases the incidence of PTB [68-70], even in women with a short cervix [71,72]. Although underpowered, the only randomized trial attempting to determine whether hospitalization of women with arrested preterm labor improved outcome found hospitalized women had a similar rate of PTB as those who were discharged home and thus presumably more active [73]. In women with a short cervix, observational studies have reported a higher rate of PTB in those with reduced physical activity [71,74].

Bed rest also has potential harms: it appears to increase the risk of thromboembolic events, has clear negative psychosocial effects, and leads to deconditioning [75-78].

**DILATED CERVIX**

Cervical dilation ≥1 cm before 24 weeks of gestation is associated with an increased risk of PTB and increasing cervical dilation is associated with increasing risk of PTB.

**Intervention**

- In women with cervical insufficiency based on physical examination, cerclage placement has been associated with a significant increase in prolongation of pregnancy and neonatal survival compared with expectant management. (See "Cervical insufficiency", section on 'Physical examination-based cervical insufficiency'.)
Multiple unrelated studies from varied disciplines (epidemiology, histopathology, microbiology, biochemistry, and maternal-fetal medicine) have reported an association between infection/inflammation and PTB, likely mediated by prostaglandins. The most consistent of these observations were reported by placental pathologists who have described histologic evidence of chorioamnionitis in the placentas of 20 to 75 percent of PTBs and positive membrane cultures in 30 to 60 percent of such patients [79-82]. In the Collaborative Perinatal Project, chorioamnionitis was detected in 6 percent of 43,940 deliveries evaluated, and the rate decreased with increasing gestational age: 15 percent at 28 to 32 weeks, 8 percent at 33 to 36 weeks, and 5 percent after 36 weeks of gestation [83].

**Asymptomatic bacteriuria** — It is unclear whether asymptomatic bacteriuria is an independent risk factor for PTB [84]. In one of the largest studies, the Cardiff Birth Survey, which prospectively studied over 25,000 births between 1970 and 1979, asymptomatic bacteriuria was not associated with a statistically significant increase in the overall rate of PTB (adjusted odds ratio [aOR] 1.21, 95% CI 0.96-1.53) [85] or sPTB (aOR 1.07, 95% CI 0.78-1.46) [86] when the data were adjusted for demographic and social factors.

**Intervention**

- A first-trimester urine culture should be performed on all pregnant women [87,88], and regular antenatal screening is recommended for women at high risk for asymptomatic bacteriuria (eg, women with sickle cell trait, recurrent urinary tract infections, diabetes mellitus, underlying renal disease). Reliance on symptoms to prompt screening is inadequate because symptoms such as frequency and nocturia are often attributed to the pregnant state.

Pregnant women with asymptomatic bacteriuria should be treated with antibiotics to reduce their risk of developing pyelonephritis and possibly to reduce the risk of PTB. In a meta-analysis (14 randomized trials), treatment of asymptomatic bacteriuria clearly and substantially decreased the frequency of asymptomatic bacteriuria (relative risk [RR] 0.25, 95% CI 0.14-0.48), pyelonephritis (RR 0.23, 95% CI 0.13-0.41) [89], and low birth weight (RR 0.66, 95% CI 0.49-0.89), but a difference in PTB was not established. (See "Urinary tract infections and asymptomatic bacteriuria in pregnancy", section on 'Asymptomatic bacteriuria'.)

**Periodontal disease** — Periodontal disease is common in adults. Two systematic reviews have reported an association between periodontal disease and adverse pregnancy outcome, such as sPTB, but did not provide conclusive evidence that pregnancy complications, including sPTB, result from periodontal disease [90,91]. The included studies had different designs and used different criteria to diagnose periodontal disease and to define adverse outcome. Moreover, they generally did not adequately adjust for confounders or have adequate sample size to detect significant differences in pregnancy outcome. Oral bacteria
that have been associated with both periodontal disease and PTB include *Tannerella forsythia*, *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Treponema denticola*, and *Fusobacterium nucleatum* [92-94].

Several hypotheses have been proposed to explain the association between periodontal disease and sPTB [95-98]. Periodontal flora may seed the fetoplacental unit and cause local inflammation, or inflammatory mediators of periodontal origin may cause systemic inflammation. An alternative, but equally reasonable, explanation is that periodontal disease is a marker of individuals who have a genetic predisposition towards an exaggerated local or systemic inflammatory response to a given stimulus (eg, bacteria), which leads to two separate adverse clinical events: periodontal disease and sPTB. Such individuals may also hyper-respond to vaginal bacteria with enhanced production of cytokines that lead to preterm labor or rupture of membranes. Thus, periodontal disease and preterm labor can be epidemiologically linked but not causally related.

**Intervention**

- Although treatment of periodontal disease contributes to oral health, there is no strong evidence that treatment of periodontal disease improves pregnancy outcome. A joint consensus report of the European Federation of Periodontology and the American Academy of Periodontology in 2013 concluded that, although periodontal therapy is safe and leads to improved periodontal health in pregnant women, periodontal therapy does not reduce overall rates of PTB and low birth weight [99]. This conclusion was based on meta-analyses limited to higher-quality randomized trials that demonstrated no significant effect of nonsurgical periodontal treatment on rates of PTB or low birth weight [100-103]. Subsequent meta-analyses have reported similar findings [104].

Several hypotheses have been proposed in an attempt to explain why periodontal treatment has not been shown to reduce risk for adverse pregnancy outcomes. Possibilities include [105]:

- Lack of causality. Periodontitis may not be a direct or indirect cause of PTB or low birth weight.

- Shared risk factors may mitigate the effect of treatment. Some risk factors for both periodontitis and poor pregnancy outcome (eg, smoking) are not affected by periodontal treatment. Furthermore, PTB is likely the end result of a variety of environmental, behavioral, social, biological, and possibly genetic factors so periodontal treatment alone is unlikely to have a major impact on reducing risk.

- Underpowered trials. Very large trials would be required to detect significant reductions in very or extreme PTB rates since these are much less common than
late PTBs.

• Lack of a consistent definition of periodontal disease. This has led to inclusion of women with mild disease whose pregnancies may not benefit from treatment.

• Treatment of periodontal disease in the trials was inadequate to affect pregnancy outcome. To demonstrate a beneficial effect, treatment may have to start before pregnancy or very early in pregnancy, continue longer, or be more intense. If PTB is related to changes in the genital tract microbiome induced by changes in the oral microbiome, local treatment of oral inflammation may not reverse genital tract changes.

*Genital tract infection/colonization* — Multiple studies have reported an association between preterm labor/delivery and various genital tract infections/colonization (table 7), including group B streptococci (GBS) [106], *Chlamydia trachomatis* [107-110], bacterial vaginosis (BV) [111-113], *Neisseria gonorrhoea* [114], syphilis [115], *Trichomonas vaginalis* [116], *Ureaplasma* species [117], and unencapsulated *Haemophilus influenzae* [118]. A positive culture correlates with the presence of histologic chorioamnionitis; however, causal relationships for most of these infections and PTB have not been proven and are controversial [106,119,120].

*Candida* species colonization is not a risk factor for PTB [121].

*Vaginal microbiome* — Emerging research has found that pregnancy alters the vaginal microbiome profile to be more hospitable to *Lactobacillus* and less favorable to *G. vaginalis* and other taxa associated with BV, with the exception of BV-associated bacterium 1 (BVAB1), which tends to remain stable [122]. In addition, there is increasing evidence that some vaginal microbiomes are associated with an increased risk for sPTB, and the prevalence of these microbiomes varies across populations [123-125]. As an example, carriage of BVAB1 is positively associated with PTB and more prevalent in pregnant women of African ancestry, who are known to have an increased risk of PTB compared with those of European ancestry, whereas carriage of *L. crispatus* is protective against PTB and more prevalent in pregnant women of European ancestry [123]. Whether interventions designed to favorably alter the vaginal microbiome will abrogate the risk of PTB is not known.

**Intervention**

• **Role of routine screening** — Some trials have reported a reduction in PTB with routine screening and treatment for infection in the early second trimester [126], while others have reported no benefit [127,128]. Discordant findings may be due to confounding by recolonization or reinfection after therapy, intercurrent use of nonprotocol antibiotics,
and failure to culture fastidious bacteria (eg, *Mycoplasma hominis, Ureaplasma urealyticum*) leading to misclassifications of women as noninfected.

**Role of empiric antibiotic therapy** – Empiric antibiotic therapy does not reduce PTB. A meta-analysis of 17 randomized trials evaluated use of prophylactic antibiotics for prevention of PTB based on abnormal vaginal flora (12 trials), a previous PTB (three trials), and a positive fetal fibronectin test result (two trials) [129]. There was no significant association between antibiotic treatment and reduction in PTB regardless of the criteria used to assess risk, the antimicrobial drug administered, or gestational age at the time of treatment (overall combined random effect for delivery at less than 37 weeks RR 1.03, 95% CI 0.86-1.24). Another meta-analysis of randomized trials limited studies of antibiotic prophylaxis in the second or third trimester also found that the intervention did not significantly reduce the risk of PTB (RR 0.85, 95% CI 0.64-1.14, five trials, 1480 women) or preterm prelabor rupture of membranes (RR 0.31, 95% CI 0.06-1.49, one trial, 229 women); however, the included studies were of low methodologic quality [130]. Subsequent randomized trials have also not shown a benefit [131].

**Chlamydia, gonorrhea, syphilis** – There is no evidence that treatment of chlamydia, gonorrhea, or syphilis prolongs gestation. The only controlled trial that evaluated the effect of treatment of chlamydia on gestational duration did not show a reduction in PTB [132]. However, screening for and treatment of these infections is recommended to prevent other maternal and neonatal sequelae. (See "Clinical manifestations and diagnosis of Neisseria gonorrhoeae infection in adults and adolescents" and "Treatment of uncomplicated Neisseria gonorrhoeae infections" and "Syphilis in pregnancy" and "Treatment of Chlamydia trachomatis infection".)

**Bacterial vaginosis, *Ureaplasma, GBS*** – Prospective controlled studies and meta-analyses have reported either a modest or no effect of antibiotic treatment on prolonging gestation in asymptomatic women who screened positive for BV [128,133-136], *Ureaplasma urealyticum* [137,138], or GBS [139], although these studies are undoubtedly confounded by recolonization or reinfection after therapy and intercurrent use of nonprotocol antibiotics. GBS screening in late pregnancy and chemoprophylaxis for prevention of early-onset neonatal GBS infection is recommended. (See "Neonatal group B streptococcal disease: Prevention".)

Women with BV and a previous PTB may benefit from BV screening and treatment, but there are insufficient data to recommend this as a routine practice. This is discussed in detail separately. (See "Bacterial vaginosis: Treatment", section on 'Pregnant'.)

**Trichomonas** – Screening and treatment of asymptomatic *Trichomonas* infection in HIV-negative women is not recommended during pregnancy because there is no convincing evidence that it reduces the risk for PTB [127,140-144]. By contrast, screening and
treatment are recommended for HIV-positive women to reduce the risks for pelvic inflammatory disease and vertical transmission of HIV [145]. (See "Trichomoniasis", section on 'Pregnant individuals'.)

**Malaria** — Malaria is associated with PTB, low birth weight, and other maternal and neonatal morbidities [146]. (See "Malaria in pregnancy: Epidemiology, clinical manifestations, diagnosis, and outcome").

**Intervention**

- Prevention of malaria infection and treatment of established malaria infection can reduce the risk for PTB [147-149]. (See "Malaria in pregnancy: Prevention and treatment").

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**BEHAVIOR**

**Short interpregnancy interval** — A short interpregnancy interval has been associated with an increased risk for PTB, even if the previous delivery was at term [150]. The risk is highest in women with a previous PTB. In a study of 263 women with consecutive sPTBs and 299 women with consecutive term births, an interpregnancy interval ≤6 months more than tripled the risk for sPTB less than 34 weeks in the second pregnancy after adjustment of confounders; the risk for late PTB was not affected [151]. (See "Interpregnancy interval: Optimizing time between pregnancies").

**Intervention**

- Increasing the interval between pregnancies to at least 12 months may reduce a woman's risk for sPTB. In a large cohort study that examined the impact of postpartum contraceptive coverage and use within 18 months of birth in preventing PTB, postpartum contraceptive coverage was protective against PTB [152]. For every month of contraceptive coverage, odds of PTB <37 weeks decreased by 1.1 percent.

  The March of Dimes encourages women to space pregnancies at least 18 months apart. However, the interval between pregnancies should not be excessive. A meta-analysis calculated that an interval ≥60 months also increased the risk for PTB (odds ratio [OR] 1.20, 95% CI 1.17-1.24) [153].

**Occupational physical activity** — A modest relationship between maternal physical activity related to working during pregnancy and PTB has been consistently noted in meta-analyses, but has not been clearly established because available evidence is generally of low quality [154-157]. Factors that have been evaluated include a high cumulative work fatigue score; standing and walking at work for more than three or four hours per day; lifting and carrying
>5 kg or ≥11 kg; lifting objects for a combined weight of ≥100 kg per day; lifting and carrying in the third trimester; having a job that required physical effort or physical exertion; and working rotating shifts, fixed night shifts, or longer hours (>40/week). The ORs ranged from 1.1 to 1.6 for all of these associations, and some dose-response patterns were observed.

It is probably important to quantitate all of the factors involved in work-related exertion, as well as the mother's ability to handle stress and fatigue, to gain insight into this controversy. In addition, a "healthy worker" effect is likely present in many studies whereby healthier workers are more likely to continue to work, work longer hours, and work in more demanding jobs, thus biasing outcomes. (See "Working during pregnancy", section on 'Work on pregnancy and child development'.)

**Intervention**

- Women with uncomplicated pregnancies who are employed where there are no greater potential hazards than those encountered in routine daily life may continue to work without interruption until the onset of labor. Nevertheless, the physical demands of the woman's job should be considered, especially in women at high risk of PTB, and working hours and occupational physical activity during pregnancy should be limited using common sense and local guidelines [158-161].

The effects of reducing occupational fatigue have not been evaluated in randomized trials. Maternity legislation in many European countries has regulated work schedules and working conditions for pregnant women; however, none of the European countries except France have experienced a reduction in PTB rates [162]. Nevertheless, paid maternity leave, guaranteed job protection, and regulation of hazardous working conditions remain desirable societal goals.

- Bed rest is **not** helpful. (See 'Bed rest is not helpful' above.)

**Exercise** — In randomized trials of women with uncomplicated pregnancies, exercise during pregnancy did not increase the risk for PTB [163]. A systematic review of prospective cohort, case-cohort, nested case-control or randomized study design found that exercise (leisure time physical activity) was not associated with an increased risk of PTB, and may decrease the risk by 10 to 14 percent compared with physical inactivity [164]. The optimum time appeared to be two to four hours of physical activity/week. As discussed above, a "healthy exerciser" effect likely exists whereby healthier women and those at low risk of PTB are more likely to continue to exercise during pregnancy. However, it has also been hypothesized that exercise may reduce the risk of PTB by reducing oxidative stress or increasing placental vascularization [165]. (See "Exercise during pregnancy and the postpartum period".)
Coitus — Sexual intercourse is not a risk factor for PTB; therefore, abstinence after pregnancy has been achieved has no role in strategies for prevention of PTB [166-169].

Smoking — Cigarette smoking has a modest dose-dependent relationship with the risk for PTB [3,85,170-176]. This effect may be explained by increased rates of smoking-related complications of pregnancy, such as placental abruption, placenta previa, prelabor rupture of membranes, and fetal growth restriction. However, the association still exists when adjustment is made for these possible confounding factors, suggesting that there may be a direct effect of cigarette smoking on spontaneous preterm labor and delivery [176]. (See "Cigarette and tobacco products in pregnancy: Impact on pregnancy and the neonate").

Intervention

- Smoking cessation should always be encouraged for its general health benefits. It is likely that smokers who decrease or stop cigarette smoking will reduce their risk for PTB, but this has not been proven. (See "Cigarette and tobacco products in pregnancy: Impact on pregnancy and the neonate", section on 'Preterm birth' and "Tobacco and nicotine use in pregnancy: Cessation strategies and treatment options").

Since 2010, in the United States, Medicaid programs are required to cover tobacco-cessation counseling and drug therapy for pregnant women without cost sharing, which might increase utilization of these services [177].

Substance use — Maternal substance use increases the risk of PTB, but it is difficult to separate the risk attributable to the substance from other risk factors, which are common in these patients [85,173-176,178-182]. In one study, women with cocaine-positive urine samples were at fourfold increased risk of developing preterm labor [180]. Another series found positive urine toxicology in 24 of 141 (17 percent) of women with preterm labor compared with 3 of 108 (2.8 percent) controls with uncomplicated labor at term [179]. Cocaine was the most common substance identified and was detected in approximately 60 percent of women in preterm labor with positive toxicology tests. Alcohol [181,183] and toluene [182] are additional substances associated with an increased risk of preterm labor and birth. In women who use multiple drugs, risk of PTB has been reported to range from 25 to 63 percent [184,185]. (See "Substance use during pregnancy: Screening and prenatal care" and "Alcohol intake and pregnancy").

Intervention

- Health care providers should attempt to identify maternal substance use, provide information on the maternal and fetal risks associated with this practice, and help patients to stop using these drugs. It is likely that this will reduce their risk for PTB, but this has not been proven. (See "Substance use during pregnancy: Screening and
Women with adequate nutrition and a normal body mass index have better pregnancy outcomes than other women, which suggests that nutritional interventions may have a role in preventing PTB in selected populations.

There is some evidence supporting the hypothesis that maternal undernutrition in pregnancy results in PTB [186]. In sheep, moderate maternal undernutrition around the time of conception results in accelerated maturation of the fetal hypothalamic-pituitary-adrenal axis, a precocious fetal cortisol surge, and PTB [187,188]. In Gambian women, pregnancies conceived during the rainy season when food is scarce were significantly shorter than those conceived when food was more plentiful [189]. Observations of shorter gestational length with early pregnancy exposure to the Dutch famine also support this hypothesis [190]. Thus, focusing on dietary events around the time of conception may be important in prevention of some cases of PTB.

**Intervention**

- In systematic reviews, isocaloric protein supplements [191], balanced protein/energy supplements [192], and high protein supplements [192] did not reduce the rate of PTB. Most studies show that vitamin supplements during pregnancy do not reduce the risk of PTB [193-199], although they have other benefits. There may be potential benefits of micronutrient supplementation in specific subpopulations of pregnant women, such as those who are undernourished or HIV-infected [200].

- In a 2018 meta-analysis of placebo-controlled randomized trials of omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) supplements or dietary additions during pregnancy, n-3 PUFA reduced PTB <37 and <34 weeks, with a corresponding trend for reduction in perinatal death [201]. These and subsequent discordant data and recommendations regarding fish consumption and n-3 PUFA supplementation during pregnancy are discussed in detail separately. (See "Fish consumption and marine omega-3 fatty acid supplementation in pregnancy".)

**WEIGHT AND WEIGHT CHANGES**

Extremes of prepregnancy weight and/or body mass index have been associated with increased rates of PTB [202-205]. The strength of this association is not well-defined because
the effect is bimodal as opposed to linear and because of interdependent variables [206]. For example, low prepregnancy weight may be confounded by socioeconomic status, race/ethnicity, and even weight gain in pregnancy.

Obese pregnant women are at increased risk of iatrogenic PTB resulting from medical complications. Obesity also appears to increase the risk for preterm prelabor rupture of membranes (PPROM) and may increase the risk of sPTB without PPROM. A potential effect on sPTB is hypothesized to be mediated by the inflammatory state, but data are weak. (See "Obesity in pregnancy: Complications and maternal management", section on 'Indicated and spontaneous preterm birth'.)

Low and high weight gain during pregnancy have also been associated with PTB [207-209]. These issues are discussed in detail separately. (See "Gestational weight gain").

**Intervention**

- Although some evidence suggests that weight loss in obese women before pregnancy and appropriate weight gain in pregnancy can reduce the risk for PTB, the evidence is not definitive. In a meta-analysis of randomized trials of the effects of dietary and lifestyle interventions in pregnancy on maternal weight and obstetric outcomes, the reduction in PTB was not statistically significant (relative risk 0.78, 95% CI 0.60-1.02, 13 trials, 2652 women) [210]. However, these trials had significant heterogeneity and were of low quality. (See "Obesity in pregnancy: Complications and maternal management" and "Gestational weight gain".)

- Regardless of its effect on pregnancy, weight loss before pregnancy should be recommended for obese women because of general health benefits. (See "Overweight and obesity in adults: Health consequences".)

- Women with eating disorders can also benefit from intervention to achieve a normal weight. (See "Eating disorders in pregnancy".)

**HEIGHT**

Women with shorter stature appear to be at increased risk for PTB and taller women appear to be decreased risk [211-213].

**STRESS**

Most women report experiencing at least one stressful life event in the year before giving birth [214]. An association between stress (including posttraumatic stress disorder) and PTB
is biologically plausible. There is evidence that maternal and fetal stress activates cells in the placenta, decidua, and fetal membranes to produce corticotropin-releasing hormone (CRH) \[^{215}\]. CRH can enhance local prostaglandin production, which initiates contractions. However, studies have not consistently demonstrated a relationship between maternal stress, CRH concentration, and PTB \[^{216-218}\]. (See "Spontaneous preterm birth: Pathogenesis", section on 'Stress-induced premature activation of the HPA axis'.)

When maternal psychosocial stress has been associated with an increased risk of PTB, the risk was modest: odds ratio 1.42 (95% CI 1.05-1.91) in cohort studies \[^{219}\]. Analysis of data is complicated by difficulty defining and measuring maternal stress, assessments at different times during pregnancy, variations in adjustment of confounders, lack of differentiation between acute and chronic stressors, and discordant baseline characteristics of the populations studied \[^{220}\].

**Intervention**

- Although social support during pregnancy has resulted in improvements in immediate psychosocial outcome, it has not been shown to significantly reduce the rate of PTB in stressed gravida. A systematic review concluded that social support was not sufficiently powerful to improve the obstetric outcome of the pregnancy in which it was provided, possibly because of the immense social deprivation experienced by most of the women in the trials examined \[^{221}\].

- There are limited data on other interventions for reducing stress in pregnant women (eg, relaxation or mind-body therapies [eg, meditation, massage, yoga, breathing exercises, music therapy, aromatherapy]). Available trials are small and of poor quality; clear effects on birth outcomes have not been proven \[^{222}\].

**ENVIRONMENT**

Systematic reviews have reported an association between PTB and fine particulate matter and ozone in the air, high environmental temperature, and phthalate exposure \[^{223-230}\]. Although the effects were small and limited by differences in study designs, particularly assessment of exposure, a causal effect is possible. (See "Occupational and environmental risks to reproduction in females: Specific exposures and impact".)

**SUBOPTIMAL PRENATAL CARE**

The absence of prenatal care has been consistently identified as a risk factor for preterm labor and delivery, but it is less clear whether this association is causal or a marker for other
factors that contribute to PTB. (See "Prenatal care: Initial assessment" and "Prenatal care: Second and third trimesters".)

**Intervention**

- Regular prenatal care should be encouraged and improves perinatal outcome in women with underlying medical disorders (eg, diabetes, chronic hypertension, thyroid disease) or pregnancy-related conditions (eg, preeclampsia); however, the March of Dimes trial discussed below suggests enhanced care is unlikely to decrease the incidence of PTB.

Retrospective studies cannot be adequately controlled to adjust for confounding factors, while randomized trials (no prenatal care versus standard care) would be unethical. Therefore, the only well-designed studies on the effect of prenatal care on PTB compare standard with enhanced care (ie, some combination of patient education, case management, home visits, nutrition counseling, and extra prenatal visits and cervical examinations).

The March of Dimes Multicenter Prematurity Prevention Trial assigned 2395 women with singleton or multiple gestations at high risk for PTB to either standard of care or an enhanced care intervention (more frequent prenatal visits, improved patient education regarding symptoms and signs of preterm labor, and weekly pelvic examinations after 20 to 24 weeks of gestation) [13]. There was no significant difference between the two groups in sPTB rates. A meta-analysis that included three trials of women with singleton pregnancies also found no clear evidence that specialized antenatal clinics reduced PTB [231].

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**PRETERM LABOR**

Uterine contractions are an essential component of labor, but mild irregular contractions are a normal finding at all stages of pregnancy, thereby adding to the challenge of distinguishing true labor (contractions that result in cervical change) from false labor (contractions that do not result in cervical change [ie, Braxton-Hicks contractions]). Only 13 percent of women presenting at <34 weeks of gestation and meeting explicit contraction criteria for preterm labor deliver within one week. (See "Preterm labor: Clinical findings, diagnostic evaluation, and initial treatment".)

**Intervention**

- Tocolytic therapy of an acute episode of idiopathic preterm labor often abolishes contractions temporarily but does not remove the underlying stimulus that initiated the process of parturition (eg, infection, inflammation, uterine overdistention, decidual hemorrhage, cervical insufficiency) or reverse parturitional changes in the uterus. The
net effect is that tocolytics are unlikely to prolong pregnancy by weeks or months. However, short-term tocolysis is endorsed by most guidelines since delivery can often be delayed for at least 48 hours, thus enabling maternal administration of glucocorticoids to achieve the maximum fetal effect [67]. (See "Inhibition of acute preterm labor" and "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery".)

**FETAL FACTORS**

Male sex is a risk factor for sPTB [232-235]. Certain congenital anomalies [236,237] and growth restriction [238-243] are risk factors for sPTB and indicated PTB.

**PATERNAL RISK FACTORS**

No paternal risk factors for development of PTB in their partners have been identified [244]. PTB risk does not appear to be affected by the father’s history of preterm children with other women or PTBs to members of the father’s family [245].

**PREDICTING RISK FOR PRETERM BIRTH**

**Risk scoring systems** — Risk scoring is a quantitative method used to identify women at increased risk for PTB. Proposed systems typically calculate an additive score based on points assigned to arbitrarily selected or weighted epidemiologic, historical, and clinical risk factors [85,175,176,178].

Systematic reviews have concluded that there is no effective risk scoring system for prediction of PTB [246,247]. This is due to our lack of knowledge regarding the cause(s) of PTB in most women and because the most powerful risk factor is previous PTB, which is not applicable to nulliparous women. The positive predictive value (the percent of women defined as high risk that actually go on to have a PTB) of most risk scoring systems is low, 20 to 30 percent, and varies according to the population studied [179].

**Biomarkers** — Cervicovaginal fetal fibronectin (fFN) can be a useful biomarker for predicting PTB within 7 to 14 days in women with contractions and mild cervical dilation and effacement, particularly when combined with ultrasound assessment of cervical length and when a quantitative measurement is available. The predictive value of fFN for PTB more than 14 days after testing is poor. (See "Preterm labor: Clinical findings, diagnostic evaluation, and initial treatment", section on '<34 weeks of gestation'.)
Fetal fibronectin may be useful for predicting risk of PTB in asymptomatic high-risk women (eg, previous PTB). A fFN $\geq$50 ng/mL at 22 to 27+6 weeks of gestation had sensitivity 55 percent and positive predictive value 27 percent for prediction of PTB <34 weeks in one study [248]. An algorithm combining quantitative fFN (not available in the United States) and cervical length, demographic information, and obstetric history (whether previous sPTB/preterm prelabor rupture of membranes or current suspected preterm labor) has been incorporated into an App (QUiPP) for prediction of sPTB in Europe [249,250].

By contrast, fFN is not useful as a screening test for predicting risk of PTB in asymptomatic nulliparous women. In the largest prospective cohort study of use of fFN in asymptomatic low-risk nulliparous women with singleton pregnancies and cervical length >15 mm (n = 9410), the sensitivity and positive predictive value of fFN $\geq$50 ng/mL at 22 to 30 weeks of gestation for PTB <32 weeks was 32.1 and 3.1 percent, respectively [251]. Using a lower or higher threshold did not significantly improve overall test performance.

A test (PreTRM Test) for two serum proteins, insulin-like growth factor-binding protein 4 and sex hormone-binding globulin, is available for clinical use to predict PTB. In a study to develop and validate a mass spectrometry-based serum test to predict spontaneous preterm delivery in asymptomatic pregnant women, the test had sensitivity and specificity of 0.75 and 0.74, respectively, for predicting PTB <37 weeks [252]. We recommend not moving forward with serum screening for PTB until such screening has been adequately tested and validated.

Over 30 other biomarkers have been studied for identification of asymptomatic women at high risk of PTB. A systematic review of these biomarkers included 72 observational studies involving almost 90,000 women and concluded that none of these other biomarkers (alone or in combination) was clinically useful for predicting sPTB in asymptomatic women [253]. The markers included inflammation-related biomarkers, placental protein/hormone-related biomarkers, angiogenesis-related biomarkers, coagulation-related biomarkers, genetic-biomarkers, and proteomic-related biomarkers.

### PROMISING INTERVENTIONS UNDER INVESTIGATION

**Low-dose aspirin** — We do not routinely prescribe low-dose aspirin for prevention of sPTB. It has been hypothesized that low-dose aspirin may reduce the risk of sPTB by inhibition of the inflammatory and uteroplacental ischemia pathways leading to this outcome (see "Spontaneous preterm birth: Pathogenesis"). Secondary outcomes from prevention of preeclampsia trials provided the initial support for this hypothesis:

- In a 2017 meta-analysis of individual participant data from trials that evaluated use of antiplatelet agents in women at high risk for developing preeclampsia (17 trials, n =
28,797 women), antiplatelet agents reduced the risk of sPTB <34 weeks of gestation (relative risk [RR] 0.86, 95% CI 0.76-0.99) and also <37 weeks [254].

- In a secondary analysis of data from a randomized trial of use of low-dose aspirin in healthy nulliparous women at low risk for developing preeclampsia, low-dose aspirin reduced the rate of sPTB <34 weeks (odds ratio 0.46, 95% CI 0.23-0.89, after adjustment for variables such as body mass index, race, tobacco use, marital status, and education level) but not sPTB <37 weeks [255].

Subsequently, the ASPIRIN trial evaluated the use of low-dose aspirin for prevention of PTB as the primary outcome [256]. Nearly 12,000 nulliparous women with singleton pregnancies in six low- and middle-income countries were randomly assigned to receive 81 mg aspirin or placebo beginning at 6+0 to 13+6 weeks of gestation and continuing until 36+6 weeks. Aspirin reduced PTB <37 weeks (11.6 versus 13.1 percent, RR 0.89, 95% CI 0.81-0.98) and <34 weeks (3.3 versus 4.0 percent, RR 0.75, 95% CI 0.61-0.93) and also reduced fetal loss and perinatal mortality; other maternal or neonatal outcomes were similar between groups. These benefits occurred, in part, because of a 60 percent reduction in women who delivered before 34 weeks with a hypertensive disorder of pregnancy (0.1 versus 0.4 percent); the incidence of hypertensive disorders in late pregnancy was not reduced. Limitations of the trial included lack of data on the effect of aspirin in women who are multiparous, carrying a multiple gestation, living in a high-income country, or residing in an area where low-dose aspirin is routinely recommended for women at moderate or high risk for developing preeclampsia. The trial also did not distinguish between sPTB and indicated PTB.

We agree with the American College of Obstetricians and Gynecologists' guidelines, which were published before the ASPIRIN trial, that state that low-dose aspirin should not be used in an attempt to prevent sPTB but should be considered for women with risk factors for preeclampsia [257]. Although it is likely that the bulk of the putative beneficial effects of low-dose aspirin on PTB is via the prevention of indicated PTB due to preeclampsia, the possibility of an effect on sPTB as well is plausible and should be studied further.

## PROGNOSIS

### Long-term maternal consequences

- **Cardiovascular disease** – Women who deliver preterm are at increased risk for cardiovascular morbidity and mortality years after the delivery. It is unclear why sPTB appears to be a marker for later cardiovascular disease or whether women who deliver preterm should be identified by primary care providers and encouraged to optimize modifiable risk factors for cardiovascular disease more so than women without this history. (See "Overview of primary prevention of cardiovascular disease".)
• In a meta-analysis of 10 cohort studies, women who had a sPTB were at higher risk for the following cardiovascular events when compared with women who delivered at term and followed for 12 to 35 years postpartum [258]:
  - Fatal and nonfatal ischemic heart disease (hazard ratio [HR] 1.38, 95% CI 1.22-1.57)
  - Fatal and nonfatal stroke (HR 1.71, 95% CI 1.53-1.91)
  - Fatal and nonfatal overall cardiovascular disease (HR 2.01, 95% CI 1.52-2.65)

• Others have shown that the risk increases with earlier PTB. In a national cohort study from Sweden, women who delivered preterm or extremely preterm had 2.5- and 4-fold increased risks of ischemic heart disease in the next 10 years compared with those who delivered full-term, even after adjusting for other maternal factors including preeclampsia, diabetes, obesity, and smoking [259].

  • **All-cause mortality** – In a national cohort study with over 50 million person-years of follow-up and over 76,000 deaths (median age at death 57.6 years), the adjusted HR (aHR) for all-cause mortality associated with preterm versus full term delivery (39 to 41 weeks) was aHR 1.73, 95% CI 1.61-1.87 during the 10 years after delivery, and increased with decreasing gestational age at preterm delivery (aHR 2.20 for preterm delivery at 22 to 27 weeks, 2.28 for preterm delivery at 28 to 33 weeks, 1.52 for preterm delivery at 34 to 36 weeks, and 1.19 for early term delivery at 37 to 38 weeks) [260]. The risks declined but remained significantly raised up to 40 years later. Several causes were identified, including cardiovascular and respiratory disorders, diabetes, and cancer, and were independent of shared genetic or environmental factors within families.

**Offspring prognosis**

  • (See "Short-term complications of the preterm infant".)
  • (See "Incidence and mortality of the preterm infant".)
  • (See "Late preterm infants".)
  • (See "Long-term outcome of the preterm infant".)
  • (See "Long-term neurodevelopmental outcome of preterm infants: Epidemiology and risk factors".)

**SOCIETY GUIDELINE LINKS**

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Preterm labor and birth".)
INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Preterm labor (The Basics)"

- Beyond the Basics topics (see "Patient education: Preterm labor (Beyond the Basics)" and "Patient education: Bacterial vaginosis (Beyond the Basics)" and "Patient education: Management of a cervical biopsy with precancerous cells (Beyond the Basics)"

SUMMARY AND RECOMMENDATIONS

There are many risk factors for preterm labor and delivery (table 2). Some are reversible, others are permanent. Identification of risk factors for spontaneous preterm birth (sPTB) before conception or early in pregnancy ideally would lead to interventions that could help prevent this complication.

- Prior PTB is the strongest risk factor for future PTB, and recurrences often occur at the same gestational age. The frequency of recurrent PTB is 15 to 30 percent after one PTB and up to 60 percent after two PTBs. Term births decrease the risk of PTB in subsequent pregnancies (table 3 and table 4). (See 'History of spontaneous preterm birth' above.)

- For women with a history of sPTB, progesterone supplementation reduces the risk of recurrent sPTB by approximately 30 percent. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth", section on 'Candidates for progesterone supplementation'.)

- Short cervical length on transvaginal ultrasound examination between 18 and 24 weeks of gestation in the current pregnancy is a risk factor for PTB and is the basis for
screening for a short cervix in the midtrimester. (See 'Short cervix' above.)

- For women with no previous history of sPTB who develop a short cervix, progesterone supplementation may prolong gestation. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth", section on 'Candidates for progesterone supplementation'.)

- For women with a history of sPTB who develop a short cervix despite progesterone supplementation, placement of a cerclage may prolong gestation. (See "Cervical insufficiency".)

- Interventions that have general health benefits and may reduce risk of PTB include smoking cessation, treatment of drug misuse, treatment of asymptomatic bacteriuria, and maintenance of a normal body mass index. (See 'Smoking' above and 'Substance use' above and 'Asymptomatic bacteriuria' above and 'Weight and weight changes' above.)

- Avoiding an interpregnancy interval of less than six months, and ideally less than 12 months, may reduce a woman's risk for sPTB. (See 'Short interpregnancy interval' above.)

- Singleton gestations are less likely to deliver preterm than multiple gestations. Prevention and reduction of multifetal gestations, particularly high-order multifetal gestations, can reduce the risk of PTB. (See 'Multifetal gestation' above.)

- We do not prescribe low-dose aspirin for prevention of sPTB, in agreement with the American College of Obstetricians and Gynecologists' guidelines. We prescribe low-dose aspirin for pregnant women with moderate or high risk factors for preeclampsia to reduce their risk for that disorder and its sequelae, which includes PTB. (See 'Low-dose aspirin' above and "Preeclampsia: Prevention", section on 'Low-dose aspirin'.)

- No biomarker performs well as a screening test for predicting sPTB in asymptomatic low risk women. (See 'Biomarkers' above.)

- Women who deliver preterm are at increased risk for cardiovascular morbidity and mortality and all-cause mortality for years after the delivery. (See 'Long-term maternal consequences' above.)

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44. Genc MR, Witkin SS, Delaney ML, et al. A disproportionate increase in IL-1beta over IL-1ra in the cervicovaginal secretions of pregnant women with altered vaginal microflora


75. Kovacevich GJ, Gaich SA, Lavin JP, et al. The prevalence of thromboembolic events among women with extended bed rest prescribed as part of the treatment for

https://www.uptodate.com/contents/6761/print


177. http://www.cdc.gov/mmwr/volumes/65/wr/mm6532a4.htm?s_cid=mm6532a4_e.


214. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6409a3.htm?s_cid=mm6409a3_e.


Topic 6761 Version 116.0
**Definitions for preterm birth**

<table>
<thead>
<tr>
<th>Gestational age criteria</th>
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</thead>
<tbody>
<tr>
<td><strong>World Health Organization</strong></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>&lt;37 weeks</td>
</tr>
<tr>
<td>Moderate to late preterm</td>
<td>32 to &lt;37 weeks</td>
</tr>
<tr>
<td>Very preterm</td>
<td>28 to &lt;37 weeks</td>
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<tr>
<td>Extremely preterm</td>
<td>&lt;28 weeks</td>
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<td><strong>Centers for Disease Control and Prevention</strong></td>
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<tr>
<td>Preterm</td>
<td>&lt;37 weeks</td>
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<tr>
<td>Late preterm</td>
<td>34 to &lt;37 weeks</td>
</tr>
<tr>
<td>Early preterm</td>
<td>&lt;34 weeks</td>
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<table>
<thead>
<tr>
<th>Birth weight criteria</th>
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<tbody>
<tr>
<td>Low birth weight (LBW)</td>
<td>&lt;2500 grams</td>
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<tr>
<td>Very low birth weight (VLBW)</td>
<td>&lt;1500 grams</td>
</tr>
<tr>
<td>Extremely low birth weight (ELBW)</td>
<td>&lt;1000 grams</td>
</tr>
</tbody>
</table>

The lower gestational age limit of preterm birth is 20+0 weeks of gestation. A birth <20 weeks of gestation is called a pregnancy loss, miscarriage, or spontaneous abortion in the United States. Preterm births are described by gestational age, birth weight, and initiating factor (e.g., spontaneous preterm birth versus medically indicated preterm birth).

Graphic 113391 Version 2.0
### Risk factors for preterm birth

#### Prior OB/GYN history
- Prior PTB
- Prior cervical surgery (eg, cone biopsy, LEEP)
- Multiple D&Es
- Uterine anomalies

#### Maternal demographics
- <17 or >35 years of age
- Lower educational level (eg, <12 grades)
- Single marital status
- Lower socioeconomic status
- Short interpregnancy interval (eg, <6 months)
- Other social factors (eg, poor access to medical care, physical abuse, acculturation)

#### Nutritional status/physical activity
- BMI <19 kg/m² or prepregnancy weight <50 kg (<120 lb)
- Poor nutritional status
- Long working hours (eg, >80 hours/week)
- Hard physical labor (eg, shift work, standing >8 hours)

#### Current maternal/pregnancy characteristics
- Conception by assisted reproductive technology (eg, IVF)
- Multiple gestation
- Fetal disorder (eg, chromosome anomaly, structural abnormality, growth restriction, death, etc)
- Vaginal bleeding (eg, 1st and 2nd trimester, placenta previa, abruption)
- Poly- or oligohydramnios
- Maternal medical conditions (eg, hypertension, diabetes, thyroid disease, asthma, etc)
- Maternal abdominal surgery during pregnancy
- Psychological issues (eg, stress, depression)
  - Substance use:
    - Smoking (eg, tobacco)
    - Heavy alcohol consumption
    - Cocaine
    - Heroin
- Infection:
  - Bacterial vaginosis
  - Trichomoniasis
  - Chlamydia
  - Gonorrhea
  - Syphilis
  - Urinary tract (eg, asymptomatic bacteriuria, pyelonephritis)
  - Severe viral infection
  - Intrauterine infection
- Short cervical length between 14 and 28 weeks
<table>
<thead>
<tr>
<th>Positive fFN between 22 and 34 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine contractions</td>
</tr>
</tbody>
</table>

OB/GYN: obstetrics and gynecology; PTB: preterm birth; LEEP: loop electrosurgical excision procedure; D&E: dilation and evacuation; BMI: body mass index; IVF: in vitro fertilization; fFN: fetal fibronectin.
### Risk of recurrent spontaneous preterm birth in a second pregnancy

<table>
<thead>
<tr>
<th>Prior PTB</th>
<th>Risk of PTB in next pregnancy (%)</th>
<th>Risk of PTB before 28 weeks of gestation (%)</th>
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<tr>
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<td>0.23</td>
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<tr>
<td>Prior PTB at 23 to 27 weeks</td>
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<td>5</td>
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<td>Prior PTB at 28 to 34 weeks</td>
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<tr>
<td>Prior PTB at 35 to 36 weeks</td>
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</tbody>
</table>

PTB: preterm birth.


Graphic 58321 Version 6.0
## Risk of preterm birth in a third pregnancy

<table>
<thead>
<tr>
<th>Obstetric history</th>
<th>Risk of PTB in third pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two prior preterm births</td>
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</tr>
<tr>
<td>Both at 32 to 36 weeks</td>
<td>33</td>
</tr>
<tr>
<td>Both at less than 32 weeks</td>
<td>57</td>
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<tr>
<td>Term birth followed by PTB</td>
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</tr>
<tr>
<td>PTB followed by term birth</td>
<td>13</td>
</tr>
<tr>
<td>Two prior term births</td>
<td>5</td>
</tr>
</tbody>
</table>

These data were derived from women with spontaneous or indicated preterm birth.

PTB: preterm birth.


Graphic 73926 Version 7.0
<table>
<thead>
<tr>
<th>Patient population</th>
<th>Interventions to be considered</th>
<th>Options in next pregnancy if history-indicated cerclage was not successful (ie, preterm birth &lt;33 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with:</td>
<td>Transvaginal cerclage at 12 to 14 weeks and Hydroxyprogesterone caproate 250 mg IM weekly from 16 to 36 weeks</td>
<td>Transabdominal cerclage Hydroxyprogesterone caproate 250 mg IM weekly from 16 to 36 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 consecutive prior second-trimester losses* or ≥3 early (&lt;34 weeks) preterm births</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with:</td>
<td>Hydroxyprogesterone caproate 250 mg IM weekly from 16 to 36 weeks Serial measurement of cervical length beginning at 14 to 16 weeks and ending at 24 weeks If cervical length ≤25 mm before 24 weeks, place transvaginal cerclage</td>
<td></td>
</tr>
<tr>
<td>One prior second-trimester loss* or One or two preterm births</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM: intramuscular.
* Usually a spontaneous pregnancy loss between 16 and 27+6 weeks of gestation.

Data from: Iams JD, Berghella V. Care for women with prior preterm birth. Am J Obstet Gynecol 2010; 203:89.
Relative risk of preterm delivery as a function of cervical length

<table>
<thead>
<tr>
<th>Cervical length (mm)</th>
<th>Percentile</th>
<th>Relative risk of PTD</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>50</td>
<td>2.35</td>
<td>1.42-3.89</td>
</tr>
<tr>
<td>≤30</td>
<td>25</td>
<td>3.79</td>
<td>2.32-6.19</td>
</tr>
<tr>
<td>≤26</td>
<td>10</td>
<td>6.19</td>
<td>3.84-9.97</td>
</tr>
<tr>
<td>≤22</td>
<td>5</td>
<td>9.49</td>
<td>5.95-15.15</td>
</tr>
<tr>
<td>≤13</td>
<td>1</td>
<td>13.99</td>
<td>7.89-24.78</td>
</tr>
</tbody>
</table>

Data from an asymptomatic general obstetric population evaluated between 22 and 30 weeks of gestation with exclusion of patients with multiple gestations, fetal anomalies, cerclage, or placenta previa. Relative risk is in comparison to patients whose cervical lengths were above the 75th percentile.

PTD: preterm delivery.


Graphic 56052 Version 7.0
## Risk of preterm birth with selected infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial vaginosis before 16 weeks</td>
<td>7.55 (1.8-31.7)</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoea</em></td>
<td>5.31 (1.57-17.9)</td>
</tr>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>2.08 (1.45-3.03)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td></td>
</tr>
<tr>
<td>at 24 weeks</td>
<td>2.2 (1.03-4.78)</td>
</tr>
<tr>
<td>at 28 weeks</td>
<td>0.95 (0.36-2.47)</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>1.3 (1.1-1.4)</td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
<td>1.0 (0.8-1.2)</td>
</tr>
</tbody>
</table>


Graphic 63047 Version 7.0
Pathogenesis of spontaneous preterm birth

Hemorrhage into the decidua (abruption) generates thrombin, which binds to PARs to activate the ERK1/2 MAP kinase signaling cascade, which directly inhibits PR expression in decidual cells and activates COX-2 to increase PGF-2alpha production. The latter contributes to ERK1/2-mediated inhibition of PR expression, which triggers contractions and directly promotes increased MMP-3 activity, causing a proteolytic cascade that degrades fetal membranes to promote PROM, and induces cervical change. Decidual inflammation associated with ascending genital tract infections with or without chorioamnionitis generates IL-1beta, which binds to its receptor to also activate the ERK1/2 MAP kinase signaling cascade inhibiting decidual cell PR expression. In addition, IL-1beta activates COX-2 and releases MMPs via the NF-kappaB signaling pathway. Premature maturation of the fetal HPA axis or maternal or fetal stress causes increased circulating cortisol (glucocorticoid), which binds to its receptor to increase levels of the immunophilin co-chaperone protein, FKBP51. Increased FKBP51 binds to both the GR and PR to decrease their transcriptional activity (functional progesterone withdrawal). Thus, ultimately COX-2 is activated and MMP-3 released to promote PTB.


Courtesy of Charles J Lockwood, MD.

Graphic 59393 Version 6.0
Contributor Disclosures


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Conflict of interest policy

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