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Preterm Labor

— Preterm birth (PTB) is the leading cause of infant morbidity and mortality in the industrialized world. For this reason, the pathogenic processes leading to PTB and development of preventive interventions are major targets of obstetric research.

Pthogenesis of spontaneous preterm birth

Compelling clinical and research evidence suggest that a number

of pathogenic processes can lead to a ommon pathway that results in spontaneous PTB. The four most common processes are:

- Premature activation of the maternal or fetal hypothalamic-pituitary-adrenal axis related to stress
- Exaggerated inammatory response/infection and/or an altered genital tract microbiome
- Abruption (decidual hemorrhage)
- Pathologic uterine distention

ACTIVATION OF THE HPA AXIS

Stress is a common element activating a series of physiologic adaptive responses in the maternal and fetal compartments. From this perspective, premature activation of the hypothalamic-pituitary-adrenal (HPA) axis can initiate PTB

- Uteroplacental ischemia is a fetal stressor that can lead to premature fetal HPA activation and has a higher correlation with subsequent PTB than maternal psychosocial stress .In one study, spontaneous PTB ≤35 to 36 weeks of gestation was associated with a four- to sevenfold increased risk of histologic evidence of placental vascular damage, bleeding, fetal vascular disruption, or lack of normal physiologic conversion of maternal spiral arteries.

The mechanisms by which fetal HPA activation are thought to cause labor, including spontaneous PTB, include:

- Increased placental production and release of corticotropin-releasing hormone (CRH), which appears to program a "placental clock" .
- Glucocorticoid induction of the immunophilin cochaperone FK506-binding protein-51 (FKBP51), which binds to the ligand binding site on the progesterone receptor (PR) and glucocorticoid receptor (GR) to inhibit PR- and GRmediated transcription in decidual cells
- Increased release of fetal pituitary adrenocorticotropic hormone (ACTH) secretion, which stimulates production of placental estrogenic compounds and prostaglandins that may activate the myometrium and initiate labor.

Placental corticotropin-releasing hormone

- CRH appears to play a role in both PTB and term birth. CRH is released by the hypothalamus but, during pregnancy, is also expressed by placental and chorionic trophoblast, amniochorion, and decidual cells .It stimulates the secretion of ACTH from the pituitary, which then promotes the release of cortisol from the adrenal. In the maternal HPA axis, cortisol inhibits hypothalamic CRH and pituitary ACTH release, creating a negative feedback loop. By contrast, cortisol stimulates CRH release in the decidua-trophoblast-membrane compartment. CRH, in turn, further drives maternal and fetal HPA activation, establishing a potent positive feedback loop.

- CRH also enhances prostaglandin production by amnion, chorion, and decidua .In turn, prostaglandins stimulate CRH release from the placenta creating a second positive feedback loop for CRH secretion.

- In a normal pregnancy, it is hypothesized that maturation of the fetal HPA axis and development of the fetal zone of the fetal adrenal gland beginning in midgestation cause a physiologic increase in fetal cortisol secretion and enhancing CRH release from the placenta .The effects of CRH are augmented near term by a reduction in maternal plasma CRH-binding protein .

- As noted above, the CRH-induced increases in maternal and fetal adrenal cortisol synthesis and placental prostaglandin production promote positive feedback loops that lead to even higher levels of CRH, cortisol, and prostaglandins .There is also some evidence that CRH can directly augment myometrial activation.

- The rise in prostaglandins ultimately results in parturition via the elaboration of genital tract proteases (eg, matrix metalloproteinases) and enhanced myometrial contractility .In vitro studies of human decidual cells suggest that prostaglandin F2-alpha, but not prostaglandin E2, can inhibit PR mRNA and protein expression .Indeed, since prostaglandins can induce labor at virtually any point in gestation, their generation is an integral part of the common final pathway of PTB.

- If the sequence of events outlined above occurs too early in gestation, preterm labor and PTB may result

- Increased fetal adrenal zone size correlates with enhanced adrenal activity, and increased fetal adrenal gland volume, as measured by ultrasound, is a potential predictor of stress-associated prematurity .However, since the fetal adrenal zone is not well developed until the third trimester, fetal stress-associated PTB is more likely to account for later PTBs.

FKBP51 expression in decidual cells

- Glucocorticoids enhance FKBP51 expression, which, in turn, inhibits PR- and GR-mediated transcription. Immunohistochemical staining for FKBP51 is elevated in the nuclei of decidual cells from patients with labor compared with prelabor specimens.

Fetal pituitary ACTH and placental estrogen production

- Activation of the fetal HPA axis also leads to PTB through a pathway involving estrogens. Fetal pituitary ACTH secretion stimulates adrenal synthesis of dehydroepiandrosterone sulfate (DHEA), which is converted to 16-hydroxyDHEA-S in the fetal liver. Placental CRH can also augment fetal adrenal DHEA production directly .The placenta converts these androgen precursors to estrone (E1), estradiol (E2), and estriol (E3), which, in the presence of estrogen receptor-alpha (ER-alpha), activate the myometrium by increasing gap junction formation, oxytocin receptors, prostaglandin activity, and enzymes responsible for muscle contraction (myosin light chain kinase, calmodulin).

Moreover, the functional progesterone withdrawal noted above is expected to be accompanied by rising concentrations of myometrial ER-alpha, thereby exacerbating estrogen-induced myometrial activation.

INFECTION, INFLAMMATION, AND ALTERED GENITAL TRACT MICROBIOME

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Inammation is a highly coordinated process set in place to protect

the host .When properly controlled, inammation is benecial, but when dysregulated, it becomes harmful .

Lactobacillus is the predominant ora of the microbial community in normal pregnancy, and the prevalence of a Lactobacillus-poor vaginal community state type (CST 4) is inversely correlated with gestational age at delivery .In addition, the risk for PTB is more pronounced for women with CST 4 and elevated Gardnerella or Ureaplasma. However, treatment of BV does not appear to consistently reduce PTB rates in low-risk patients .

- Similarly, periodontal disease and subsequent systemic inammation may play a role in triggering PTB .Intervention studies have not consistently demonstrated a benet to treatment .However, it remains possible that the putative benecial eects of periodontal treatment may be dependent on time of initiation and success of therapy.

Furthermore, chorioamnionitis is associated with intense decidual immunostaining for IL-8 and CSF-2, which recruit neutrophils capable of releasing additional preterm prelabor rupture of membranes (PPROM)causing MMPs, and IL1beta and/or TNF greatly augment the output of IL-8 and CSF-2 in term decidual cells .TNF-alpha plays an additional role since it can induce apoptosis (physiologic cell death). Elevated levels of TNF and increased apoptosis in amnion epithelial cells have been associated with PPROM.

Thus, both maternal and fetal inammatory responses to infection are processes that can lead to preterm labor and PPROM. By contrast, the presence of bacteria, without a host response, does not always cause an adverse outcome .

Bacteria

In addition to inducing an inammatory response, bacteria may also have a direct role in the pathogenesis of PTB. Some organisms (eg, Pseudomonas, Staphylococcus, Streptococcus, Bacteroides, and Enterobacter) produce proteases, collagenases, and elastases that can degrade the fetal membranes .Bacteria also produce phospholipase A2 (which leads to prostaglandin synthesis) and endotoxin, substances that stimulate uterine contractions and can cause preterm labor .

Proinflammatory mediators unrelated to infection

Noninfectious etiologies, such as placental hypoperfusion, also appear to increase production of proinflammatory mediators .This may be another mechanism accounting for the slightly higher rate of spontaneous PTB among growth restricted infants.

In addition, there is increasing evidence that psychological stress and distress (ie, depressive symptoms) can cause dysregulation of inflammatory processes leading to elevations in circulating inflammatory cytokines and exaggerated inflammatory responses.

DECIDUAL HEMORRHAGE

Vaginal bleeding from decidual hemorrhage is associated with a high risk of preterm labor and preterm prelabor rupture of membranes (PPROM) .Decidual hemorrhage (placental abruption) originates in damaged decidual blood vessels and presents clinically as vaginal bleeding or retroplacental hematoma formation.

In a case-control study of 341 patients, vaginal bleeding in more than one trimester increased the risk of PPROM sevenfold .In another series, occult decidual hemorrhage (manifested by hemosiderin deposition and retro-chorionic hematoma formation) was present in 38 percent of patients with PTB between 22 and 32 weeks of gestation due to PPROM and 36 percent of patients experiencing PTB after preterm labor; these placental ndings were present in only 0.8 percent of term deliveries.

The development of PPROM in the setting of abruption may be related to the high decidual cell expression of tissue factor, the primary cellular mediator of hemostasis. Following intrauterine hemorrhage from placental abruption, decidual tissue factor combines with factor VIIa to activate factor Xa, which in turn complexes with its cofactor, Va, to generate thrombin .In addition to its hemostatic properties, thrombin binds to decidual protease-activated receptors (PAR1 and 3) that upregulate the expression of proteases such as matrix metalloproteinases (MMPs).

Decidual hemorrhage results in intense local thrombin generation. Hormonal factors such as progesterone play an important modulator role .Thrombin also induces synthesis of elements of the fibrinolytic system in decidual cells .However, the primary eect of thrombin is to inhibit fibrinolysis via generation of type-1 plasminogen inhibitor (PAI-1) to avoid hemorrhage in the setting of abruption, suggesting that abruption-associated decidual proteolysis and PPROM are mediated primarily by thrombin-enhanced MMP expression.

PATHOLOGIC UTERINE DISTENTION

Multiple gestation, polyhydramnios, and other causes of excessive uterine distention are well described risk factors for PTB. Enhanced stretching of the myometrium induces formation of gap junctions, upregulation of oxytocin receptors, and production of inflammatory cytokines and prostaglandins, and myosin light chain kinase, which are critical events preceding uterine contractions and cervical dilation .

Myometrial distention also increases expression of genes with important roles in collagenolysis and inammation . Distention of the fetal membranes also contributes to myometrial activation. Cytokines, prostaglandins, and collagenase are produced from excess membrane stretch.

PATHOLOGIC CERVICAL CHANGE

Cervical insuciency refers to pathologic dilatation and/or eacement of the uterine cervix unrelated to labor and leading to previable pregnancy loss, as well as PTB. It may occur with or without coexisting distention of the corpus, and cerclage may be helpful in select instances.

- Cervical insufficiency due to intrinsic cervical factors is probably a rare event. It is more likely that progressive cervical shortening prior to viability results from activation of the inflammatory of hemorrhagic pathways at a point in gestation when both myometrial quiescence, as well as amniotic fluid, fetal membrane, and decidual antiprotease activity are maximal. Thus, cervical change occurs without apparent antecedent preterm labor and preterm prelabor rupture of membranes.

GENETICS OF PRETERM BIRTH

PTB demonstrates familial aggregation. Women who were themselves born prematurely have a higher risk of PTB, and the risk of PTB increases by 80 percent in women whose sisters had PTB. A variety of single nucleotide polymorphisms, the majority associated with inflammation, have been linked to PTB.

Risk factors

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. Women at highest risk are those with:
- No term pregnancy between the previous sPTB and the current pregnancy
- A history of multiple sPTBs

- 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. 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 thanwomen with a history of preterm prelabor rupture of membranes or preterm labor. (55 versus 27 versus 32 percent,respectively) .
- The increased risk remained after adjustment for gestational age of the last PTB.

- 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% CI5.5-11.2)

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.
- 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).

History of abortion

- In a systematic review of pregnancy outcome after uterine evacuation including over one million women (31studies 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.Women who underwent medical termination of pregnancy had a similar future risk of PTB as women with no history of pregnancy termination.
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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 .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 .In addition, concordance for timing of parturition is higher in women who are monozygotic twins than in those who are dizygotic twins .
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NON-HISPANIC BLACK RACE

- In the United States, non-Hispanic Black women consistently have a higher rate of PTB than non-Hispanic White women .In a meta-analysis of eight English-language studies including over 26 million singleton births, the odds ofPTB 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 (OR1.37), Black mother/Black father (OR 1.78) .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 .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 .Women's race/ethnicity seems to influence their microbiome and the impact of vaginal bacteria on PTB .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). Alternatively, immune hyporesponsiveness may create a permissive environment for ascending infection and its sequelae (premature labor, PPROM).

AGE

- The rate of PTB is higher at the extremes of maternal age .Physiologic immaturity and socioeconomic factors may increase risk for dolescent 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.

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 echanisms include loss of tensile strength from loss of cervical stroma, increased usceptibility for infection from loss of cervical glands, and loss of cervical plasticity from cervical scarring.

UTERINE MALFORMATIONS

Congenital

- In women with congenital uterine malformations, the magnitude of risk for PTB depends upon the specific abnormality.

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.

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.

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.

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.

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.

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) [58]. In this and other studies, the association was stronger for PTB before 34 weeks than late PTB [58,59]. 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.

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 .A high Bishop score on digital examination is also associated with increased odds of PTB.

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.

INFECTION

- 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.

Asymptomatic bacteriuria

- It is unclear whether asymptomatic bacteriuria is an independent risk factor for PTB .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) or sPTB (aOR 1.07, 95% CI 0.78-1.46) when the data were adjusted for demographic and social factors.

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 .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.*

Genital tract infection/colonization

- Multiple studies have reported an association between preterm labor/delivery and various genital tract infections/colonization, including group B streptococci (GBS) *Chlamydia trachomatis* , bacterial vaginosis (BV), *Neisseria gonorrhea*, syphilis, *Trichomonas vaginalis*, *Ureaplasma* species, and unencapsulated *Haemophilus influenzae*. 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.
- *Candida* species colonization is **not** a risk factor for PTB

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 .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 .

Malaria

Malaria is associated with PTB, low birth weight, and other maternal and neonatal morbidities.

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 .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.

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 .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, ffxed 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.

Exercise

- In randomized trials of women with uncomplicated pregnancies, exercise during pregnancy did not increase the risk for PTB .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 .

- 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.

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.

Smoking

Cigarette smoking has a modest dose-dependent relationship with the risk for PTB .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.

Substance use

- Maternal substance use increases the risk of PTB, but it is dificult to separate the risk attributable to the substance from other risk factors, which are common in these patients. In one study, women with cocaine positive urine samples were at fourfold increased risk of developing preterm labor. 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 .
- Cocaine was the most common substance identified and was detected in approximately 60 percent of women in preterm labor with positive toxicology tests. Alcohol and toluene 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.

DIET

- 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 .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 .In Gambian women, pregnancies conceived during the rainy season when food is scarce were significantly shorter than those conceived when food was more plentiful .
- Observations of shorter gestational length with early pregnancy exposure to the

Dutch famine also support this hypothesis .Thus, focusing on dietary events around the time of conception may be important in prevention of some cases of PTB.

WEIGHT AND WEIGHT CHANGES

- Extremes of prepregnancy weight and/or body mass index have been associated with increased rates of PTB. The strength of this association is not well-defined because the effect is bimodal as opposed to linear and because of interdependent variables .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 alsoappears 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 inffammatory state, but data are weak.
- Low and high weight gain during pregnancy have also been associated with.These issues are discussedPTB in detail separately.

HEIGHT

Women with shorter stature appear to be at increased risk for PTB and taller women appear to be decreased risk.

STRESS

- Most women report experiencing at least one stressful life event in the year before giving birth .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 corticotropinreleasing hormone (CRH) .CRH can enhance local prostaglandin production, which initiates contractions.However, studies have not consistently demonstrated a relationship between maternal stress, CRH concentration, and PTB .
- 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 .Analysis of data is complicated by diffculty 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.

ENVIRONMENT

Systematic reviews have reported an association between PTB and ozone particulate matter and ozone in the air and between PTB and heat exposure .Although the effect was small and limited by differences in study designs, particularly assessment of exposure, a causal effect is possible.

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.

FETAL FACTORS

Male sex is a risk factor for sPTB .Certain congenital anomalies and growth restriction are risk factors for sPTB and indicated PTB.

PROGNOSIS

- **Long-term maternal consequences**

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.

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 .

- **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.

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) .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.

INFORMATION FOR PATIENTS

- UpToDate o?ers 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 ve 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.

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 'Spontaneous singleton preterm birth in prior pregnancy'.)
- 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 'Shortcervix' above.)

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