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The State of the Science of Preterm Birth

Assessing Contemporary Screening and Preventive Strategies

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ABSTRACT

Preterm birth remains a leading cause of morbidity and mortality during the perinatal and neonatal periods. Now affecting approximately 1 in 10 births in the United States, preterm birth often occurs spontaneously and without a clear etiology. Careful assessment of risk factors, however, identifies vulnerable women allowing targeted interventions such as progestogen therapy and cerclage. This article is intended to highlight preterm birth risk factors and current predictive and preventive strategies for midwives, nurse practitioners, clinical nurse specialists, and perinatal nurses.

Key Words: cerclage, cervical length, preterm birth, prevention, progesterone, risk factors, spontaneous

Preterm birth (PTB), a live birth occurring prior to 37 weeks' gestation,[1] remains a serious global health problem. The implications of being born preterm are profound for the individual, families, and society as a whole, with prematurity identified as a leading cause of neonatal mortality worldwide.[2]

Despite significant expenditures on healthcare, the United States ranks sixth among the top 10 countries with the greatest number of PTBs, accounting for more than 42% of those in high-income regions.[3] While rates in the United States declined by 8% from 2007 to 2014, there has been an increase in recent years.[4,5] In 2018, the PTB rate rose for the fourth straight year, now impacting 1 in 10 infants born in the United States.[6]

In this time of great uncertainty, there is a critical need to understand the state of the science as it relates to PTB—what is known, what works, and what lies beyond the horizon. In this regard, midwives, nurse practitioners, clinical nurse specialists, and perinatal nurses who span the spectrum of women's care play a critical role. The purpose of this review is to assess risk factors and current predictive and preventive strategies for perinatal clinicians to reduce the incidence of spontaneous PTB.

IDENTIFYING AT RISK WOMEN

All women contemplating pregnancy are assessed for PTB risk factors. In general, risk factors with an odds ratio (OR) or relative risk (RR) of 2-3 or greater are most impactful. While scoring systems quantifying a woman's risk are available, there is currently no widely accepted tool that effectively predicts PTB; a thorough history remains the best strategy.[7] Preterm birth risk factors are categorized as nonmodifiable or modifiable. Modifiable causes may be reduced with interventions before conception or during pregnancy. In this regard, a preconception counseling appointment is particularly useful. At this visit, the clinician should recommend normalization of an increased body mass index and optimization of other medical comorbidities to reduce medically indicated PTB rates.[8] Among couples with

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infertility, assisted reproductive technology with single embryo transfer reduces the incidence of twins and higher-order multiples, which are more likely to birth preterm.[9] Finally, appropriate timing of pregnancy is recommended, given that short intervals, especially those less than 6 months, may increase PTB risk.[10] Table 1 lists both the major modifiable and nonmodifiable PTB risk factors and the recommended interventions for each.

MODIFIABLE RISK FACTORS FOR PTB

Interpregnancy interval

Interpregnancy interval refers to the time between the end of one pregnancy and a new conception. There is no universally accepted definition on what defines an appropriate interpregnancy interval. The March of Dimes, for example, recommends at least 18 months for all women while the World Health Organization advises waiting at least 24 months following a live birth.[11,12] Evidence demonstrating an association between short interpregnancy intervals and an increased risk for PTB, however, is modest and generally limited to very short intervals. A 2018 systematic review of 27 studies reported that an interpregnancy interval less than 6 months was associated with a statistically significant (albeit minor) increased risk of PTB with an adjusted OR of 1.20 or greater in 10 of 14 studies included.[10] The implications of a very short interpregnancy interval on PTB may be most pronounced in already vulnerable populations (such as African Americans) due in part to disparities in health and access to medical care.[13]

Asymptomatic bacteriuria

Asymptomatic bacteriuria occurs in 2% to 10% of pregnant women, with gram-negative bacterium *Escherichia coli* being the most commonly implicated pathogen.[14] If left untreated, women with asymptomatic bacteriuria may develop an ascending infection such as pyelonephritis, which is an independent risk factor for preterm labor.[15]

Table 1. Preterm birth risk factors and recommended interventions

Risk factor	Impact on PTB (reported OR and/or RR)	Recommended intervention
Interpregnancy interval	Minimal (OR ≥1.2 with intervals <6 mo)	Preconception and contraceptive counseling Appropriately timed interval
Asymptomatic bacteriuria	Minimal (unclear in isolation, OR = 1.3 for pyelonephritis)	Universal screening in first trimester Treatment if ≥100 k CFU Repeat culture
Tobacco use	Minimal but dose dependent (OR = 1.5 with >20 cigarettes per day in second trimester)	Counseling on cessation Promote partner cessation Consider pharmacotherapy for refractory use
Cervical insufficiency	Significant but difficult to quantify separate from prior preterm birth in general (not available)	History-indicated cerclage (transvaginal) Consider transabdominal cerclage if prior cerclage failure 17P
Genital infections	Potentially significant but varies on the basis of pathogen and gestational age of exposure (OR = 2-8)	Universal screening in first trimester Treatment with test of cure/reinfection Rescreen in third trimester
Recreational drug use	Significant (OR = 2-3)	Counseling on cessation
Short cervix (<20 mm)	Significant (RR = 3-6)	Vaginal progesterone Consider cerclage for overt dilation, severe shortening (<10 mm), or progressive shortening on progesterone
Prior preterm birth	Significant (OR = 5-6)	Detailed history 17P if prior spontaneous PTB Cervical length monitoring 16-23 wk if prior spontaneous PTB <34 wk with cerclage if shortening
Multiple gestations	Significant (OR = 6-10)	Optimize prenatal care Individualize cervical length surveillance, cerclage placement, and progesterone

Abbreviations: CFU, colony-forming unit; OR, odds ratio; PTB, preterm birth; RR, relative risk; 17P, 17-α hydroxyprogesterone caproate.

Asymptomatic bacteriuria's effect on PTB, independent of progression to pyelonephritis, is unclear. While smaller studies initially demonstrated an association, the Cardiff Birth Survey, which prospectively evaluated more than 25 000 births, concluded that asymptomatic bacteriuria was not associated with a significant increase in the overall PTB rate (OR = 1.21; 95% confidence interval [CI], 0.96-1.53) or spontaneous PTB (OR = 1.07; 95% CI, 0.78-1.46).[16,17] More recently, a 2018 Cochrane systematic review classified treatment of asymptomatic bacteriuria as a "possible benefit" to prevent PTB based on limited evidence.[18] Hence, screening and treatment of asymptomatic bacteriuria may be regarded as an addressable but less impactful intervention for preventing PTB.

Genital tract infections

Maternal genital tract infections, including bacterial vaginosis and some sexually transmitted infections, are associated with PTB. However, like asymptomatic bacteriuria, causal relationships between these infections and PTB are lacking.[19–21] In a large meta-analysis, bacterial vaginosis increased PTB risk more than twofold (OR = 2.19; 95% CI, 1.54-3.12), and women at highest risk were those diagnosed prior to 16 weeks' gestation (OR = 7.55; 95% CI, 1.80-31.65).[22] Sexually transmitted genital tract infections including *Neisseria gonorrhea* (gonorrhea) and *Chlamydia trachomatis* (chlamydial infection) have also been linked to PTB. Available data suggest a stronger and more consistent association between chlamydial infection and PTB (OR = 2.28; 95% CI, 1.64-3.16) than gonorrhea, with data for the latter pathogen being conflicting and difficult to separate from other risk factors.[20,21] As a result of this and other adverse pregnancy effects, the United States Preventive Services Task Force (USPSTF) recommends screening all sexually active women younger than 25 years and those older than 25 years with additional risk factors for gonorrhea and chlamydial infection.[23]

Cigarette use

While tobacco use continues to decline, an estimated 7.2% of expectant mothers smoked in 2016.[24] There is high-quality evidence that smoking cigarettes adversely affects pregnancy duration with approximately 5% to 8% of all PTBs attributed to smoking.[25] While the pathophysiology of this relationship is not completely understood, it is thought that impaired gas exchange, increased oxidative stress, and direct maternal and fetal exposure to toxins lead to altered fetal development and sympathetic responses.[26]

The link between cigarette smoking and PTB appears to be dose dependent. For example, a recent cross-sectional study showed that among first-trimester smokers, the odds of PTB were 1.16 times higher for those who smoked 1 to 9 cigarettes per day, 1.24 times higher for those who smoked 10 to 19 cigarettes per day, and 1.30 times higher for those who smoked 20 or more cigarettes per day compared with nonsmokers. Similarly, the odds of PTB among second-trimester smokers increased as 1.58 times higher for those who smoked 10 to 19 cigarettes per day.[27] New-onset smoking in a second pregnancy has also been shown to double PTB risk compared with nonsmokers.[28] In addition, placenta previa, abruption, premature rupture of membranes, fetal growth restriction, and sudden infant death syndrome all occur more frequently in cigarette users.[29]

Electronic vapor products (also known as electronic cigarettes or e-cigarettes) have recently grown in popularity. These devices rely on an electronic delivery system that aerosolizes nicotine, producing a vapor similar to traditional cigarettes but with fewer toxins.[30] In a nationally representative survey, approximately 3% of women aged 18 to 44 years used an electronic vapor product, with similar use rates between pregnant and nonpregnant women.[31] Adverse pregnancy outcomes linked to vaping and other smokeless tobacco products (snuff, chewing tobacco) have been reported, but data are limited with respect to these products' overall safety including in pregnancy. While the short- and long-term effects of vaping are the focus of ongoing investigation, the Centers for Disease Control and Prevention reported that more than 2000 cases of severe lung illnesses were associated with the practice in 2019. The etiology of these illnesses is unknown, though refilled e-cigarette cartridges obtained via informal or illicit sources may be a factor.[32] It is recommended that any product that exposes pregnant women and by extension, a fetus to nicotine and other harmful or potentially harmful substances should be avoided.

Recreational drugs

Like cigarette smoking, maternal recreational drug use appears to increase PTB. However, isolating risks attributable to chemical substances, legal and illegal, from confounding factors such as low socioeconomic status and concurrent cigarette use is difficult. A 2019 study with more than 2 million subjects evaluated an association between maternal drug use and PTB in a population of singleton live births in California. Rates of PTB varied from 11.6% among cannabis users to 24.3% for those abusing cocaine, compared with 6.7% in reported nonusers.[33] A systematic review and meta-analysis of more than 30 studies confirmed that cocaine use during pregnancy was associated with a significantly higher

chance of PTB compared with nonusers with a reported OR of 3.38 (95% CI, 2.72-4.21).[34]

NONMODIFIABLE RISK FACTORS FOR PTB

Significant risks for PTB that are not modifiable include prior birth(s) before 37 weeks' gestation, shortened cervix and cervical insufficiency, race, ethnicity, and maternal age. The strongest predictor of spontaneous PTB is a history of a prior birth before 34 weeks' gestation (reported ORs of 5-6).[4,35] In all women with a prior PTB, gathering additional history concerning clinical presentation, pregnancy management, birth outcomes, and suspected etiology is key. Obtaining prenatal, hospital, and neonatal records including autopsy reports if available may also be useful.

A mid-trimester shortened cervix identified by transvaginal ultrasonography (TVUS) is a significant PTB risk factor (RR = 3-6), as cervical length serves as a surrogate measurement for effactment.[36,37] Since effacement begins at the internal cervical os and progresses distally, shortening can be detected on ultrasound scan earlier than physical examination. In many women, early shortening of the cervix may be a sign of impending cervical insufficiency, which often leads to previable birth.[38] Cervical insufficiency specifically describes the inability of a cervix to retain a pregnancy due to intrinsic structural weakness of cervical tissue. This weakness may be congenital (such as in women with collagen vascular disorders) or acquired, which may occur after cervical excision procedures.[39]

Preterm birth rates vary by ethnicity and race. A systematic review and meta-analysis from 2013 identified no significant association between Asian, Hispanic, or Latina ethnicities and spontaneous PTB.[40] However, rates are nearly 2 times higher among non-Hispanic black women than among white women, with a reported OR of 1.78.[40,41]

Maternal age is another nonmodifiable risk factor for PTB. Women at the extremes of childbearing age are at a higher risk of delivering preterm, though for different reasons.[42] Younger women have higher rates of spontaneous PTB while older women tend to have higher rates of medically indicated PTB, likely due to the higher incidence of hypertension, use of assisted reproductive technologies, pregestational diabetes, and invasive procedures in pregnancy in this population.[42] Women 30 to 34 years of age have the lowest rates of PTB.[42]

Finally, women with multiple gestations are at a significant risk for spontaneous PTB, and preterm delivery in twins and triplets occurs at rates 7.5 and 12.3 times higher than singletons.[6] More specifically, the PTB rates for twins, triplets, and quadruplets are 59%, 99%, and 100%, respectively.[43] A multiple gestation is a potentially modifiable risk factor via single embryo transfer in pregnancies conceived with assisted reproductive technology or by multifetal reduction, particularly in higher-order multiples.[44,45]

PTB PREVENTION STRATEGIES

Treatment of asymptomatic bacteriuria

Recommendations by the USPSTF and the Infectious Diseases Society of America support screening all pregnant women for asymptomatic bacteriuria at least once in early pregnancy.[46,47] The initial prenatal visit is considered a reasonable time to obtain a urine culture and treat if necessary. Antibiotic treatment is indicated for women with urine colony counts of more than 100 000 units. Treatment for asymptomatic bacteriuria includes a short course (3-7 days) with narrow-spectrum antibiotics such as nitrofurantoin, amoxicillin, or cephalexin. Single-dose fosfomycin is also an option for treating bacteriuria. Despite recommended treatment, up to 30% of women fail to clear asymptomatic bacteriuria following antibiotic therapy. Therefore, a repeat culture 1 to 2 weeks after treatment is generally recommended as a test of cure. A 7- to 10-day course of culture-specific antibiotics is recommended in cases in which a short course has failed.[46]

Smoking cessation

Smoking cessation is considered one of the most impactful interventions to prevent PTB, and first-trimester and second-trimester smoking cessation can reduce the risk of PTB by 30% and 13%, respectively.[48] Current USPSTF recommendations include screening pregnant women for tobacco use, advising cessation, and providing resources such as fact sheets from the Centers for Disease Control and Prevention or the Department of Health & Human Services.[49]

Pharmacologic therapy for tobacco cessation is reserved for women who fail behavioral interventions. There is currently inadequate evidence to assess the benefits and harms of nicotine replacement products or other pharmaceuticals for smoking cessation aids during pregnancy.[49] The American College of Obstetricians and Gynecologists advises that use of nicotine replacement therapy may be undertaken with close supervision and after weighing known risks of continued smoking versus possible risks of therapy.[29] Bupropion, a dopamine norepinephrine-reuptake inhibitor used to treat depression, is also available as a smoking cessation aid. While data in pregnancy are limited, there are no known risks of fetal anomalies or adverse pregnancy effects.[29,50] Varenicline, a centrally acting agent,

specifically targets nicotine receptors. A recent systematic review demonstrated no major adverse effects from exposure in pregnancy.[51] However, due to limited data, varenicline use is not currently advised in pregnancy.

Fetal fibronectin screening

Fetal fibronectin (fFN) is an extracellular matrix glycoprotein found at the uterine-chorion interface. In uncomplicated gestations, fFN is released into cervicovaginal secretions up to 20 to 22 weeks' gestation and again after 37 weeks. Fetal fibronectin levels are low between these gestational ages. Disruption of this interface due to subclinical infection, abruption, or uterine contractions releases fFN into cervicovaginal secretions. Detection of fFN is the basis for use as a marker for predicting spontaneous PTB.[52]

Fetal fibronectin is most helpful in evaluating women with preterm labor symptoms, particularly in a setting of an equivocal cervical length. Fetal fibronectin's utility lies in its negative predictive value and ability to rule out women at risk of delivering within the following week. A large clinical trial evaluating fFN testing in women with preterm labor symptoms reported a negative predictive value for PTB within 7 days of 99.5%.[53] A positive value correlates poorly with PTB. To date, evidence does not support using fFN as a screening tool in asymptomatic women. A systematic review and meta-analysis demonstrated that fFN screening in this population lacked precision.[54]

Investigations combining qualitative and quantitative fFN with cervical length in various high-risk populations are ongoing, but available results are not promising. A prospective observational study of asymptomatic women undergoing mid-trimester cervical length assessment explored an added value of qualitative fFN. Study results concluded that while the combination increased sensitivity, predictive accuracy was not substantially improved.[55] Similarly, a study involving more than 9000 nulliparous women explored serial cervical length assessments coupled with quantitative fFN with no improved accuracy in predicting PTB.[56] Whether combining fFN with cervical length and other biomarkers will prove beneficial in select subpopulations remains unclear.

Cervical length screening

A cervical length of less than the 10th percentile is recognized as an independent predictor for PTB. Current guidelines recommend TVUS cervical assessment after a transabdominal view of the lower uterine segment if there are clinical concerns.[57,58] A transabdominal cervical length less than 35 mm identifies 100% of women with a shortened transvaginal cervical length.[57,59,60] Universal screening via TVUS is more controversial and not currently mandated by major societal guidelines; however, proponents of universal screening argue that this practice meets generally accepted guidelines of an effective tool and appears to be cost-effective.[57,61,62]

Serial cervical length monitoring is recommended in women with a prior spontaneous PTB that occurred at less than 34 weeks' gestation, and ultrasound scans are obtained from 16 weeks until viability at approximately 23 to 24 weeks. Women with a cervical length of 30 mm or greater are generally seen at 2-week intervals with a transition to weekly cervical length screening if measurements are between 25 and 29 mm.[57]

Of note, a shortened cervical length appears to be more common in multiple gestations. In a large, multicenter preterm prediction study conducted by the Maternal-Fetal Medicine Units Network, approximately 18% of twin gestations had a cervical length of less than 25 mm at 22 to 24 weeks' gestation as compared with 9% of singletons. Preterm birth risk with cervical lengths less than 25 mm was increased eightfold in twins versus sixfold in singletons.[63] Because cervical shortening is common in multiple gestations and compelling evidence of an effective intervention is limited, professional guidelines do not currently recommend cervical length monitoring for multiple gestations.[57,61]

Cervical pessary

While supporting evidence is limited, an obstetric pessary is thought to prevent PTB by altering the cervical canal axis, displacing fetal weight from the internal cervical os.[64] A recent meta-analysis that evaluated efficacy of an Arabin cervical pessary for preventing spontaneous PTB in singleton gestations with second-trimester cervical lengths of 25 mm or less did not result in statistically significant reductions in spontaneous PTB at 37, 34, 32, or 28 weeks' gestation compared with no pessary.[65]

Conflicting results were found in 2 trials that included women with singleton gestations, cervical shortening on TVUS, and no history of spontaneous PTB. One trial failed to show value with using a pessary compared with no pessary, while another study reported a benefit (RR = 0.48; 95% CI, 0.24-0.95).[64,66] A subsequent study involving women with cervical shortening reported that pessaries were noninferior to vaginal progesterone for preventing PTB before 34 weeks' gestation.[67] In total, evidence to date on use of pessary for prevention of PTB has not matched initial expectations.

Cerclage

There are 3 indications for cerclage placement: a clinical history consistent with cervical insufficiency, a

shortened cervix noted on transvaginal ultrasound scan, or mid-trimester cervical dilation absent preterm labor symptoms or infectious concerns. A cerclage involves placement of a permanent purse-string suture transvaginally via the McDonald or Shirodkar technique. A transabdominal approach, either by laparotomy or minimally invasively, is an alternative reserved for women who either fail a transvaginal cerclage or who have anatomic limitations.[38]

Women with a pregnancy history of cervical insufficiency may benefit from a cerclage. In appropriately counseled women, procedures may occur between 12 and 14 weeks to reinforce a cervix and mechanically prevent dilation.[38] If TVUS demonstrates cervical shortening less than 25 mm between 16 and 24 weeks in a woman with a prior spontaneous PTB before 34 weeks, placement of an ultrasound-indicated cerclage is recommended. Although data are limited, cerclage placement in this population reduces PTB risk and by extension improves composite perinatal morbidity and mortality.[38,68]

In selected cases, cerclage has been shown to be a potential adjunct to vaginal progesterone, specifically for women with severe cervical shortening or those who continue to have decreasing cervical length despite this medication. In a systematic review and meta-analysis with planned subgroup analysis, PTB prior to 35 weeks' gestation in women with extreme cervical shortening (defined as <10 mm) was reduced from 58% to 39.5% with cerclage placement.[69] A retrospective cohort study included women who were started on vaginal progesterone with an incidentally shortened cervix of less than 20 mm. A subset of women with progressive shortening to less than 10 mm received a cerclage. Individuals with cerclages gave birth at a later gestational age than those on vaginal progesterone alone (34 + 3 vs 27 + 2, $P < .001$).[70]

Occasionally, women without PTB risk factors will develop cervical dilation in the absence of preterm labor or infection. Physical examination-indicated or rescue cerclage is an option in this group of women.[38] A meta-analysis of 10 studies demonstrated pregnancy prolongation by an average of 33 days and improved neonatal survival compared with no cerclage in this population.[71] Unsurprisingly, rescue cerclages are associated with increased rates of complications and failure compared with history or ultrasound-indicated procedures.

Cerclage placement in unselected multiple gestations does not appear to confer benefit, and an ultrasound-indicated cerclage is not recommended in twin gestations by the American College of Obstetricians and Gynecologists due to a lack of benefit and concern for potential harm.[38,72,73] There may be a role for the placement of a history or physical examination-indicated cerclage in select twin gestations; however, given the limited supporting evidence, shared decision making is recommended. Figures 1 and 2 summarize the integration of cervical length surveillance, progestogens, and cerclage into patient care based on fetal number.

Progestogens

Two progestogen agents are commonly used in women at increased risk for PTB: vaginal progesterone and intramuscular 17-α hydroxyprogesterone caproate (17P). If an incidentally shortened cervix is identified, mid-trimester vaginal progesterone, administered as a gel or suppository, is recommended. No adverse effects on neurodevelopmental outcome of offspring have been demonstrated with use.[74]

In a landmark study, researchers measured cervical length at a median of 22 weeks' gestation in more than 24 000 women with no history of PTB. Women with cervical lengths measured to be 15 mm or less were randomized to receive either a 200-mg vaginal progesterone suppository nightly or a placebo from 24 to 34 weeks' gestation. A significantly decreased frequency in spontaneous birth before 34 weeks' gestation in women randomized to progesterone compared with placebo was reported (19.2% vs 34.4%).[75] A follow-up randomized controlled trial confirmed that administration of 90-mg vaginal progesterone gel to women with a mid-trimester–shortened cervix on ultrasound scan reduced PTB incidence before 33 weeks' gestation by 45%, resulting in improved neonatal outcomes.[76] A 2018 systematic review and meta-analysis of data from nearly 1000 women reported that vaginal progesterone supplementation reduced PTB risk at less than 36, 35, 34, 32, 30, and 28 weeks' gestation with no adverse neonatal effects.[77] More recent evidence suggests that vaginal progesterone in twin gestations with a mid-trimester–shortened cervix reduces PTB risk before 30 and 35 weeks' gestation age and by extension neonatal mortality.[78] This may justify sonographic monitoring of cervical length in twins.

Intramuscular 17P is a US Food and Drug Administration–approved progestogen available for women with a prior spontaneous PTB.[57,79] A clinical trial enrolled 463 women with a singleton gestation with at least one prior spontaneous PTB to study the effects of compounded progesterone injections in preventing subsequent PTB. Women were randomized to either weekly injections of 17P or placebo.[70] Birth at less than 37 weeks' gestation was reduced from 54.9% to 36.3%, in addition to a decreased incidence of PTB between 35 and 32 weeks' gestation.

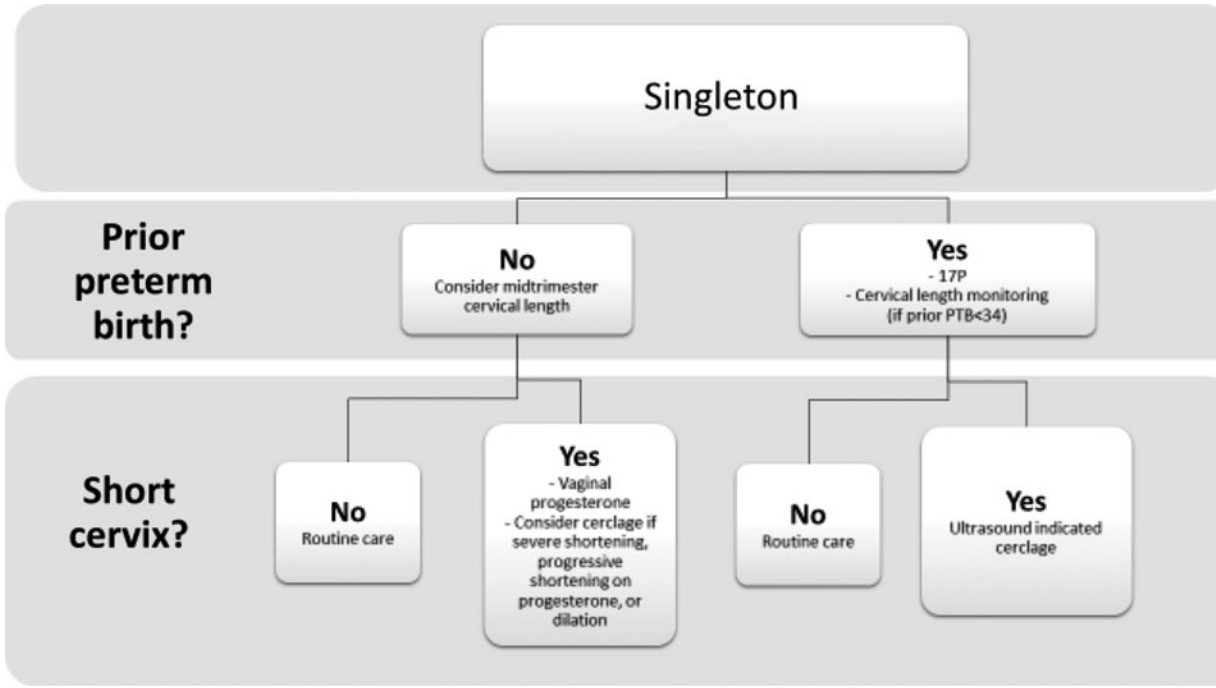

Figure 1. Recommended approach to progestogens, cervical length screening, and cerclage placement for singleton gestations. PTB indicates preterm birth; 17P, 17-α hydroxyprogesterone caproate. From Owen et al,[37] American College of Obstetricians and Gynecologists,[38] Razaz et al,[44] Committee on Practice Bulletins–Obstetrics, American College of Obstetricians and Gynecologists,[57] McIntosh et al,[61] Son et al,[62] Enakpene et al,[70] and Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella.[79]

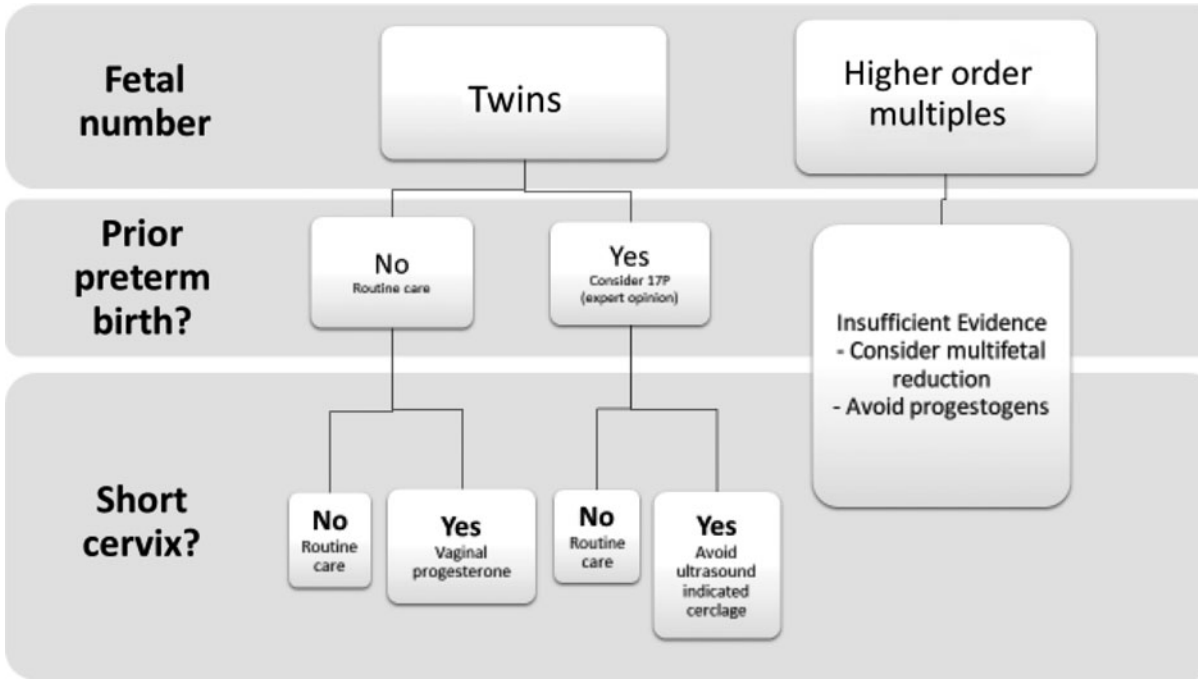

Figure 2. Recommended approach to progestogens, cervical length screening, and cerclage placement for multiple gestations. 17P indicates 17-α hydroxyprogesterone caproate. From Owen et al,[37] American College of Obstetricians and Gynecologists,[38] Razaz et al,[44] Committee on Practice Bulletins–Obstetrics, American College of Obstetricians and Gynecologists,[57] McIntosh et al,[61] Son et al,[62] Enakpene et al,[70] and Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella.[79]

Weekly injections of 250 mg are initiated at 16 to 20 weeks' gestation in women with a prior PTB and are continued until 37 weeks' gestation. Early cessation has been associated with an increased risk for PTB.[80] This medication's precise mechanism is unclear; however, progesterone may have an anti-inflammatory effect mediated by suppression of proinflammatory cytokines or prevent cell death in fetal membranes.[81–83]

Approval of this medication by the US Food and Drug Administration in 2011 was contingent on the Progestin's Role in Optimizing Neonatal Gestation (PROLONG) follow-up study to confirm efficacy. Study results were released in late 2019 revealing no statistically significant reduction in the primary outcomes of PTB before 35 weeks or composite neonatal morbidity and mortality.[84] Currently, there is no change in major societal guidelines regarding the use of 17P, but these results compared with prior published data are under review and the ultimate decision regarding ongoing approval by the US Food and Drug Administration is unknown.[85,86] Hence, these results may have a profound impact on pregnancy management of this high-risk cohort.

DISCUSSION

Despite considerable expenditures, extensive research, and implementation of interventions, the spontaneous PTB rate remains frustratingly immovable. Challenges relating to this condition span the entire healthcare system from research laboratories to clinical practice. Fundamentally, the precise mechanisms leading to spontaneous PTB are unknown despite ongoing research into potential genomic, molecular, and metabolic causes.

At the bedside, proven interventions are often delayed or not implemented at all. A retrospective cohort study conducted at a single academic center reported that only 69.3% of at-risk women received counseling on progesterone therapy with 36.1% of those eligible receiving at least 1 dose of 17P.[87] In a separate study, non-Hispanic black women (a cohort at highest risk for PTB) were more likely to start progesterone therapy later in their pregnancy and miss doses than other groups.[88] A recent study evaluating obstetrician adherence to national guidelines relating to PTB prevention found poor compliance despite efforts at better dissemination.[89] At the end of 2019, the results of the much anticipated "PROLONG" trial questioned the very benefit of intramuscular progestogen, long regarded as the most effective preventive strategy in high-risk women.[84]

In spite of these challenges, there is hope on the horizon. Development and implementation of specialty clinics and evidence-based care bundles have improved outcomes in other areas of medicine such as chronic obstructive pulmonary disease and infection prevention with the potential to do the same for PTB.[90,91] Frustrated by inconsistencies in practice and implementation of evidence-based measures, a large US hospital's birth center formed a multidisciplinary committee to optimize the evaluation and management of women presenting with concern for preterm labor. Implementation of standing order sets, group rounds, and a dedicated care coordinator resulted in standardization of practice and reduced hospital length of stay.[92] In another healthcare system, enacting a protocol-based approach to cervical length screening, prescribing progestogens, and triaging women presenting with preterm labor symptoms resulted in a significant decrease in the incidence of PTBs.[93] Finally, an analysis of 70 dedicated recurrent PTB prevention clinics demonstrated a significant reduction in subsequent PTB and neonatal morbidity compared with facilities providing usual care.[94]

When PTB does occur, implementation of bundles containing proven interventions such as antenatal corticosteroids can mitigate the neonatal impact. In Tanzania, a pilot study assessed the benefits of a low-cost, evidence-based care bundle on preterm infant mortality. Execution of the bundle (at a cost of approximately US $6-$7 per infant) resulted in a significant reduction in preterm deaths, neonatal mortality, and stillbirths.[95] Standardizing care and maximizing the use of established interventions have the potential to have a truly

Table 2. Selected preterm birth prevention resources

	Suggested resources
Practice guidelines	American Academy of Family Physicians (www.aafp.org) American College of Obstetricians and Gynecologists (www.acog.org) Society for Maternal-Fetal Medicine (www.smfm.org) World Health Organization (www.who.org)
Research and education	March of Dimes (www.marchofdimes.org) National Institute of Child Health and Human Development (www.nih.nichd.gov) Preterm Birth International Collaborative (www.prebicglobal.org)
Clinical tool kits	March of Dimes (www.marchofdimes.org) Society for Maternal-Fetal Medicine (https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit)

profound impact on PTB on a global scale. An estimated 500 000 neonatal deaths occurred in sub-Saharan Africa in 2015; however, a mathematical model exploring better implementation of WHO-recommended interventions reported that nearly 300 000 deaths could have been prevented.[96] Table 2 lists suggested resources for practice guidelines, research and education, and tool kits.

In the laboratory, researchers are studying the effect of existing and novel agents in reducing the expression of cytokines thought to play a key role in inflammation-induced PTB. Statins, a widely used drug class to lower cholesterol, possess anti-inflammatory properties and reduce contraction of smooth muscle cells. Repurposing these agents to treat preterm labor has shown promise in animal models.[97] Likewise, a novel therapy targeting a specific inflammatory pathway associated with preterm labor in laboratory studies may one day prove valuable in reducing PTB and improving neonatal outcomes in humans.[98] Finally, ongoing evaluation of the microbiome and its variations in normal pregnancy and spontaneous preterm labor may allow a more targeted, nuanced approach to antibiotic therapy.[99]

There are no immediate solutions to dramatically decrease PTB rates. The notion that a "one-size-fits-all" approach (such as progestogens) exists to counter a complex, heterogeneous condition seems naive in hindsight. Further reductions in the PTB rate may be achieved through a multifaceted approach incorporating health optimization, improved access to care, broader implementation of existing proven interventions, and ongoing research on novel therapies.

CONCLUSION

As leaders in women's health, perinatal nurse clinicians will continue to play a pivotal role in policy, research, and clinical care related to preterm labor and birth. Ultimately, understanding the precise mechanism(s) of spontaneous PTB is fundamental to targeting effective strategies for prevention in the future.

References

1. World Health Organization. Preterm birth. https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Published 2018. Accessed December 23, 2019.
2. Ray JG, Park AL, Fell DB. Mortality in infants affected by preterm birth and severe small-for-gestational age birth weight. *Pediatrics*. 2017;140(6):pii: e20171881.
3. World Health Organization. *Born Too Soon: The Global Action Report on Preterm Birth*. Geneva, Switzerland: World Health Organization; 2012.
4. Howson CP, Kinney MV, McDougall L, Lawn JE. Born too soon: preterm birth matters. *Reprod Health*. 2013;10(suppl 1):S1.
5. Matthews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2015;64(9):1–30.
6. Hamilton BE, Martin JA, Osterman MJK, Rossen LM. Births: final data for 2018. *Natl Vital Stat Rep*. 2019;68(13):1–47.
7. Meertens LJE, van Montfort P, Scheepers HCJ, et al. Prediction models for the risk of spontaneous preterm birth based on maternal characteristics: a systematic review and independent external validation. *Acta Obstet Gynecol Scand*. 2018;97(8):907–920. doi:10.1111/aogs.13358.
8. Parker MG, Ouyang F, Pearson C, et al. Prepregnancy body mass index and risk of preterm birth: association heterogeneity by preterm subgroups. *BMC Pregnancy Childbirth*. 2014;14:153.
9. Devine K, Connell MT, Richter KS, et al. Single vitrified blastocyst transfer maximizes liveborn children per embryo while minimizing preterm birth. *Fertil Steril*. 2015;103(6):1454–1460. e1451.
10. Ahrens KA, Nelson H, Stidd RL, Moskosky S, Hutcheon JA. Short interpregnancy intervals and adverse perinatal outcomes in high-resource settings: an updated systematic review. *Paediatr Perinat Epidemiol*. 2019;33(1):O25–O47.
11. March of Dimes Fact Sheet. Birth spacing and birth outcomes. https://www.marchofdimes.org/MOD-Birth-Spacing-Factsheet-November-2015.pdf. Published 2015. Accessed January 5, 2020.
12. World Health Organization. *Report of a WHO Technical Consultation on Birth Spacing*. Geneva, Switzerland: World Health Organization; 2005.
13. Thagard AS, Napolitano PG, Bryant AS. The role of extremes in interpregnancy interval in women at increased risk for adverse obstetric outcomes due to health disparities: a literature review. *Curr Womens Health Rev*. 2018;14(3):242–250.
14. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68(10):e83–e110.
15. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. *Am J Obstet Gynecol*. 2014;210(3):219. e211–e216.
16. Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales. I. Univariable and multivariable analysis. *Am J Obstet Gynecol*. 1995;173(2):590–596.
17. Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales. II. Indicated and spontaneous preterm birth. *Am J Obstet Gynecol*. 1995;173(2):597–602.
18. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev*. 2018;11:CD012505.
19. Mancuso MS, Figueroa D, Szychowski JM, Paden MM, Owen J. Midtrimester bacterial vaginosis and cervical length in women at risk for preterm birth. *Am J Obstet Gynecol*. 2011;204(4):342. e341–e345.
20. Ahmadi A, Ramazanzadeh R, Sayehmiri K, Sayehmiri F, Amirmozafari N. Association of Chlamydia trachomatis infections with preterm delivery; a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2018;18(1):240.
21. Heumann CL, Quilter LA, Eastment MC, Heffron R, Hawes SE. Adverse birth outcomes and maternal Neisseria gonorrhoeae infection: a population-based cohort study in Washington State. *Sex Transm Dis*. 2017;44(5):266–271.
22. Leitich H, Bodner-Adler B, Brunbauer M, Kaider A, Egarter C, Husslein P. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. *Am J Obstet Gynecol*. 2003;189(1):139–147.
23. LeFevre ML. Screening for chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161(12):902–910.

24. Drake P DA, Mathews TJ. *Cigarette Smoking During Pregnancy: United States, 2016*. Hyattsville, MD: National Center for Health Statistics; 2018.
25. Dietz PM, England LJ, Shapiro-Mendoza CK, Tong VT, Farr SL, Callaghan WM. Infant morbidity and mortality attributable to prenatal smoking in the U.S. *Am J Prev Med*. 2010;39(1):45–52.
26. Stone WL, Bailey B, Khraisha N. The pathophysiology of smoking during pregnancy: a systems biology approach. *Front Biosci (Elite Ed)*. 2014;6:318–328.
27. Soneji S, Beltran-Sanchez H. Association of maternal cigarette smoking and smoking cessation with preterm birth. *JAMA Netw Open*. 2019;2(4):e192514.
28. Wong LF, Wilkes J, Korgenski K, Varner MW, Manuck TA. Risk factors associated with preterm birth after a prior term delivery. *BJOG*. 2016;123(11):1772–1778.
29. Committee on Underserved Women, Committee on Obstetric Practice. Committee opinion no. 721: smoking cessation during pregnancy. *Obstet Gynecol*. 2017;130(4):e200–e204.
30. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Ann Intern Med*. 2017;166(6):390–400.
31. Liu B, Xu G, Rong S, et al. National estimates of e-cigarette use among pregnant and nonpregnant women of reproductive age in the United States, 2014–2017. *JAMA Pediatr*. 2019;173(6):600–602.
32. Chatham-Stephens K, Roguski K, Jang Y, et al. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury. *MMWR Morb Mortal Wkly Rep*. 2019;68:1076–1080.
33. Baer RJ, Chambers CD, Ryckman KK, Oltman SP, Rand L, Jelliffe-Pawlowski LL. Risk of preterm and early term birth by maternal drug use. *J Perinatol*. 2019;39(2):286–294.
34. Gouin K, Murphy K, Shah PS. Effects of cocaine use during pregnancy on low birth weight and preterm birth: systematic review and metaanalyses. *Am J Obstet Gynecol*. 2011;204(4):340. e1–e12.
35. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. *Am J Obstet Gynecol*. 2014;210(2):131. e1–e8.
36. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. *New Engl J Med*. 1996;334(9):567–572.
37. Owen J, Yost N, Berghella V, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA*. 2001;286(11):1340–1348.
38. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 142: cerclage for the management of cervical insufficiency. *Obstet Gynecol*. 2014;123(2, pt 1):372–379.
39. Roman A, Suhag A, Berghella V. Overview of cervical insufficiency: diagnosis, etiologies, and risk factors. *Clin Obstet Gynecol*. 2016;59(2):237–240.
40. Schaaf JM, Liem SM, Mol BW, Abu-Hanna A, Ravelli AC. Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. *Am J Perinatol*. 2013;30(6):433–450.
41. Srinivasjois RM, Shah S, Shah PS. Biracial couples and adverse birth outcomes: a systematic review and meta-analyses. *Acta Obstet Gynecol Scand*. 2012;91(10):1134–1146.
42. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: a large cohort study. *PLoS One*. 2018;13(1):e0191002.
43. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2017. *Natl Vital Stat Rep*. 2018;67(8):1–50.
44. Razaz N, Avitan T, Ting J, Pressey T, Joseph KS. Perinatal outcomes in multifetal pregnancy following fetal reduction. *CMAJ*. 2017;189(18):E652–E658.
45. Abel JS, Flock A, Berg C, Gembruch U, Geipel A. Expectant management versus multifetal pregnancy reduction in higher order multiple pregnancies containing a monochorionic pair and a review of the literature. *Arch Gynecol Obstet*. 2016;294(6):1167–1173.
46. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*. 2005;40(5):643–654.
47. Henderson JT, Webber EM, Bean SI. Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2019;322(12):1195–1205.
48. Polakowski LL, Akinbami LJ, Mendola P. Prenatal smoking cessation and the risk of delivering preterm and small-for-gestational-age newborns. *Obstet Gynecol*. 2009;114(2, pt 1):318–325.
49. Siu AL. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2015;163(8):622–634.
50. Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2015;(12):Cd010078.
51. Turner E, Jones M, Vaz LR, Coleman T. Systematic review and meta-analysis to assess the safety of bupropion and varenicline in pregnancy. *Nicotine Tob Res*. 2019;21(8):1001–1010.
52. Genc MR, Ford CE. The clinical use of inflammatory markers during pregnancy. *Curr Opin Obstet Gynecol*. 2010;22(2):116–121.
53. Deshpande SN, van Asselt AD, Tomini F, et al. Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis. *Health Technol Assess*. 2013;17(40):1–138.
54. Faron G, Balepa L, Parra J, Fils JF, Gucciardo L. The fetal fibronectin test: 25 years after its development, what is the evidence regarding its clinical utility? A systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2018;33(3):1–31.
55. Jwala S, Tran TL, Terenna C, et al. Evaluation of additive effect of quantitative fetal fibronectin to cervical length for prediction of spontaneous preterm birth among asymptomatic low-risk women. *Acta Obstet Gynecol Scand*. 2016;95(8):948–955.
56. Esplin MS, Elovitz MA, Iams JD, et al. Predictive accuracy of serial transvaginal cervical lengths and quantitative vaginal fetal fibronectin levels for spontaneous preterm birth among nulliparous women. *JAMA*. 2017;317(10):1047–1056.
57. Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol*. 2012;120(4):964–973.
58. AIUM practice parameter for the performance of detailed second- and third-trimester diagnostic obstetric ultrasound examinations. *J Ultrasound Med*. 2019;38(12):3093–3100.
59. Friedman AM, Srinivas SK, Parry S, Elovitz MA, Wang E, Schwartz N. Can transabdominal ultrasound be used as a screening test for short cervical length? *Am J Obstet Gynecol*. 2013;208(3):190. e1–e7.
60. Cho HJ, Roh HJ. Correlation between cervical lengths measured by transabdominal and transvaginal sonography for

predicting preterm birth. *J Ultrasound Med*. 2016;35(3):537–544.
61. McIntosh J, Feltovich H, Berghella V, Manuck T. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. *Am J Obstet Gynecol*. 2016;215(3):B2–B7.
62. Son M, Grobman WA, Ayala NK, Miller ES. A universal mid-trimester transvaginal cervical length screening program and its associated reduced preterm birth rate. *Am J Obstet Gynecol*. 2016;214(3):365. e361–e365.
63. Goldenberg RL, Iams JD, Miodovnik M, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*. 1996;175(4, pt 1):1047–1053.
64. Saccone G, Maruotti GM, Giudicepietro A, Martinelli P. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. *JAMA*. 2017;318(23): 2317–2324.
65. Saccone G, Ciardulli A, Xodo S, et al. Cervical pessary for preventing preterm birth in singleton pregnancies with short cervical length: a systematic review and meta-analysis. *J Ultrasound Med*. 2017;36(8):1535–1543.
66. Dugoff L, Berghella V, Sehdev H, Mackeen AD, Goetzl L, Ludmir J. Prevention of preterm birth with pessary in singletons (PoPPS): randomized controlled trial. *Ultrasound Obstet Gynecol*. 2018;51(5):573–579.
67. Cruz-Melguizo S, San-Frutos L, Martinez-Payo C, et al. Cervical pessary compared with vaginal progesterone for preventing early preterm birth: a randomized controlled trial. *Obstet Gynecol*. 2018;132(4):907–915.
68. Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet Gynecol*. 2011;117(3):663–671.
69. Berghella V, Ciardulli A, Rust OA, et al. Cerclage for sonographic short cervix in singleton gestations without prior spontaneous preterm birth: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. *Ultrasound Obstet Gynecol*. 2017;50(5): 569–577.
70. Enakpene CA, DiGiovanni L, Jones TN, Marshalla M, Mastrogiannis D, Della Torre M. Cervical cerclage for singleton pregnant patients on vaginal progesterone with progressive cervical shortening. *Am J Obstet Gynecol*. 2018;219(4):397. e391–e397. e310.
71. Ehsanipoor RM, Seligman NS, Saccone G, et al. Physical examination-indicated cerclage: a systematic review and meta-analysis. *Obstet Gynecol*. 2015;126(1):125–135.
72. Saccone G, Rust O, Althuisius S, Roman A, Berghella V. Cerclage for short cervix in twin pregnancies: systematic review and meta-analysis of randomized trials using individual patient-level data. *Acta Obstet Gynecol Scand*. 2015; 94(4):352–358.
73. Rafael TJ, Berghella V, Alfirevic Z. Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy. *Cochrane Database Syst Rev*. 2014;(9):CD009166.
74. Romero R, Nicolaides KH, Conde-Agudelo A, et al. Vaginal progesterone decreases preterm birth </= 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. *Ultrasound Obstet Gynecol*. 2016;48(3):308–317.
75. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*. 2007;357(5):462–469.
76. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol*. 2011;38(1):18–31.
77. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol*. 2018;218(2):161–180.
78. Romero R, Conde-Agudelo A, El-Refaie W, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol*. 2017;49(3):303–314.
79. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol*. 2012;206(5):376–386.
80. Rebarber A, Ferrara LA, Hanley ML, et al. Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 2007;196(3):224.e1–e4.
81. Garry DJ, Baker DA, Persad MD, Peresleni T, Kocis C, Demishev M. Progesterone effects on vaginal cytokines in women with a history of preterm birth. *PLoS One*. 2018; 13(12):e0209346.
82. Allen TK, Nazzal MN, Feng L, Buhimschi IA, Murtha AP. Progestins inhibit tumor necrosis factor alpha-induced matrix metalloproteinase 9 activity via the glucocorticoid receptor in primary amnion epithelial cells. *Reprod Sci*. 2019;26(9):1193–1202.
83. Wang Y, Abrahams VM, Luo G, et al. Progesterone inhibits apoptosis in fetal membranes by altering expression of both pro- and antiapoptotic proteins. *Reprod Sci*. 2018; 25(8):1161–1167.
84. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): a multicenter, international, randomized double-blind trial. *Am J Perinatol*. 2020;37(2):127–136.
85. Zahn CM. ACOG statement on 17p hydroxyprogesterone caproate https://www.acog.org/About-ACOG/News-Room/Statements/2019/ACOG-Statement-on-17p-Hydroxyprogesterone-Caproate?IsMobileSet=false. Published 2019. Accessed December 22, 2019.
86. Society for Maternal-Fetal Medicine. *Use of 17-Alpha Hydroxyprogesterone Caproate for Prevention of Recurrent Preterm Birth*. Washington, DC: SMFM Publications Committee; 2019.
87. DeNoble AE, Wynn CE, Weaver KE, Wheeler SM, Swamy GK. Factors associated with utilization of 17-hydroxyprogesterone caproate for the prevention of recurrent preterm birth. *Am J Perinatol*. 2019;37(3):264–270. doi:10.1055/s-0039-1678532.
88. Yee LM, Liu LY, Sakowicz A, Bolden JR, Miller ES. Racial and ethnic disparities in use of 17-alpha hydroxyprogesterone caproate for prevention of preterm birth. *Am J Obstet Gynecol*. 2016;214(3):374. e371–e376.
89. Rousseau A, Azria E, Baumann S, Deneux-Tharaux C, Senat MV. Do obstetricians apply the national guidelines? A vignette-based study assessing practices for prevention of preterm birth. *BJOG*. 2019;27(4):467–476. doi:10.1111/1471-0528.16039.
90. Lenherr Ramos L, Weber R, Sax H, Giovanoli P, Kuster SP. A comprehensive unit-based safety program for the reduction of surgical site infections in plastic surgery and hand surgery. *Infect Control Hosp Epidemiol*. 2019;40(12):1367–1373.

91. Zafar MA, Loftus TM, Palmer JP, et al. COPD care bundle in emergency department observation unit reduces emergency department revisits. *Respir Care*. 2020;65(1):1–10.
92. Goering M, Wilson W. Implementing preterm labor guidelines: a collaborative care improvement process. *J Perinat Neonatal Nurs*. 2002;16(1):47–57.
93. Knapp JM, Navathe RS, Keller N, Berghella V. Trends in preterm birth: an academic center's campaign to reduce the incidence [published online ahead of print December 3, 2019]. *J Matern Fetal Neonatal Med*. doi: 10.1080/14767058.2019.1698029.
94. Manuck TA, Henry E, Gibson J, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. *Am J Obstet Gynecol*. 2011;204(4):320. e321–e326.
95. Massawe A, Kidanto HL, Moshiro R, et al. A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country. *PLoS One*. 2018;13(3):e0193146.
96. Griffin JB, Jobe AH, Rouse D, McClure EM, Goldenberg RL, Kamath-Rayne BD. Evaluating WHO-recommended interventions for preterm birth: a mathematical model of the potential reduction of preterm mortality in sub-Saharan Africa. *Global Health Sci Pract*. 2019;7(2):215–227.
97. Boyle AK, Rinaldi SF, Rossi AG, Saunders PTK, Norman JE. Repurposing simvastatin as a therapy for preterm labor: evidence from preclinical models. *FASEB J*. Trends in preterm birth: an academic center's campaign to reduce the incidence 2019;33(2):2743–2758.
98. Gomez-Lopez N, Romero R, Garcia-Flores V, et al. Inhibition of the NLRP3 inflammasome can prevent sterile intraamniotic inflammation, preterm labor/birth, and adverse neonatal outcomes. *Biol Reprod*. 2019;100(5):1306–1318.
99. Staude B, Oehmke F, Lauer T, et al. The microbiome and preterm birth: a change in paradigm with profound implications for pathophysiologic concepts and novel therapeutic strategies. *Biomed Res Int*. 2018;2018:7218187.

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