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Prediction and Prevention of Spontaneous Preterm Birth

Preterm birth is among the most complex and important challenges in obstetrics. Despite decades of research and clinical advancement, approximately 1 in 10 newborns in the United States is born prematurely. These newborns account for approximately three-quarters of perinatal mortality and more than one half of long-term neonatal morbidity, at significant social and economic cost (1–3). Because preterm birth is the common endpoint for multiple pathophysiologic processes, detailed classification schemes for preterm birth phenotype and etiology have been proposed (4, 5). In general, approximately one half of preterm births follow spontaneous preterm labor, about a quarter follow preterm prelabor rupture of membranes (PPROM), and the remaining quarter of preterm births are intentional, medically indicated by maternal or fetal complications. There are pronounced racial disparities in the preterm birth rate in the United States.

The purpose of this document is to describe the risk factors, screening methods, and treatments for preventing spontaneous preterm birth, and to review the evidence supporting their roles in clinical practice. This Practice Bulletin has been updated to include information on increasing rates of preterm birth in the United States, disparities in preterm birth rates, and approaches to screening and prevention strategies for patients at risk for spontaneous preterm birth.

Background

Definition

Preterm birth is defined as a delivery occurring at or after 20 0/7 weeks of gestation and before 37 0/7 weeks of gestation. Preterm birth may be spontaneous (following preterm labor, PPROM, or cervical insufficiency) or it may be indicated by a specific maternal or fetal complication. Preterm birth also is divided into early and late time periods; early preterm birth occurs before 34 0/7 weeks of gestation, and late preterm birth occurs between 34 0/7 and 36 6/7 weeks of gestation.

Epidemiology

Preterm birth rates have been increasing in the United States following a decrease from 2007 to 2014 (6). In 2019, the preterm birth rate in the United States was 10.2% (7). The increase in the total preterm birth rate for 2017–2018 was driven by an increase in late preterm deliveries (34–36 weeks of gestation), up from 7.2% to 7.3% (6). The rate of early preterm birth (2.8%) has remained largely unchanged since 2014.

There are notable racial and ethnic disparities in the preterm birth rate in the United States. In 2019, White women had a preterm birth rate of 9.3%, Hispanic women had a preterm birth rate of 10%, and non-Hispanic Black women had a preterm birth rate that was about 50% higher than both, at 14.4% (Figure 1) (7). In 2018, the preterm birth rate among American Indian and Alaska Native women was 11.5%, and it was 11.8% among Native Hawaiian or other Pacific Islander women (6).

Infants born prematurely have increased risks of morbidity and death throughout childhood, especially during the first year of life (8). These risks increase for

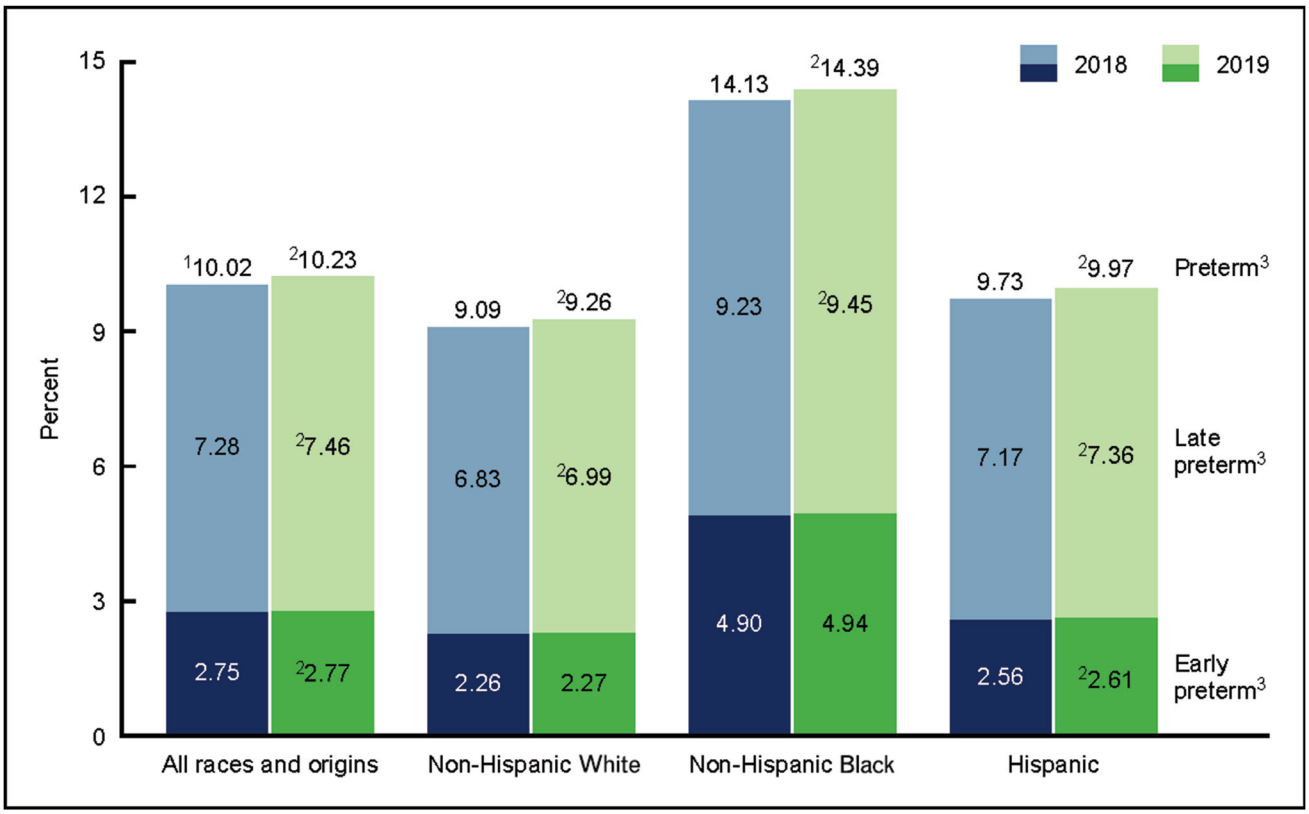

Figure 1. Preterm birth rates, by race and Hispanic origin of the mother: United States, 2018 and 2019. Reprinted from Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2019. NCHS Data Brief 2020 Oct(387):1–8. [1]Data do not add to totals due to rounding. [2]Significant increase from 2018 ($P<.05$). [3]Significant difference between all race and Hispanic-origin groups ($P<.05$). NOTES: Preterm is less than 37 weeks of gestation, late preterm is 34–36 weeks of gestation, and early preterm is less than 34 weeks of gestation. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db387-tables-508.pdf#4. SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

the individual as gestational age at birth decreases. Care for preterm infants has a significant economic effect; a review of 2016 data estimated an incremental cost of $25 billion, with higher individual costs associated with earlier gestational age at delivery (9).

Factors Associated With Spontaneous Preterm Birth

Many factors have been associated with preterm birth, including maternal demographics and characteristics, social and economic factors, medical complications, obstetric history, and conditions specific to the current pregnancy (10). Rates of preterm birth remain higher for non-Hispanic Black and Indigenous women than for White, Asian, or Hispanic women, and are not explained by social determinants of health and education (11, 12). Strikingly, preterm birth rates are higher for non-Hispanic Black women who have higher educational attainment than for non-Hispanic White, Asian, or Hispanic women with lower educational attainment. Chronic stress related to long-term exposure to structural racism is a potential explanation for the disparity in preterm birth rates between African-American or Afro-Caribbean women and women of other racial and ethnic backgrounds (13). Recognizing that race is a social rather than a biological construct, the effects of structural, institutionalized, and interpersonal racism and implicit and explicit biases implicated in many health inequities are more likely than race itself to be related to elevated risk (14, 15). Social and economic disadvantage are persistently associated with an increased risk of preterm birth: lower educational attainment; geographic residence in disadvantaged neighborhoods, states, and regions; and lack of access to prenatal care are all linked to significantly higher rates of preterm birth (16). Although many of these individual associations are statistically significant, each factor alone is not strongly associated with preterm birth (17).

Several risk factors for preterm birth are potentially modifiable, including low maternal prepregnancy weight, smoking, substance use, and short interpregnancy interval. A maternal prepregnancy body mass index (BMI) less than 18.5 has been associated with an increased risk of preterm birth (18). Tobacco use is

associated with an increased risk of preterm birth, likely through vasoconstrictive and hypoxia-mediated pathways (19, 20). A number of studies have found an interpregnancy interval of less than 18 months to be associated with preterm birth and other morbidities (21–23). Unintended pregnancies are associated with an increased risk for preterm birth (24, 25), whereas observational data at the state level in Colorado suggest that improved access to family planning services and increased use of long-acting reversible contraception (LARC) are associated with a lower rate of preterm birth (26). Thus, postpartum and prepregnancy care provide an important opportunity to assess risk factors and counsel and treat individuals with modifiable risk factors to reduce the risk of preterm birth (27, 28). The ability of health care professionals to mitigate these risks is impaired by the high rate of unplanned pregnancy in the United States and limited access to prepregnancy care for many women with risk factors.

A history of preterm birth is a very strong predictor of subsequent preterm birth (29–31). The number of prior preterm births and the degree of prematurity at the prior birth significantly affect the recurrence risk of preterm birth (32, 33). A preterm birth followed by birth at term confers lower risk than the opposite sequence (32–34). Even for patients whose prior preterm birth was a twin birth, the risk of preterm birth in a subsequent singleton gestation is increased and varies according to the gestational age at the preterm twin birth, with a recurrence risk as high as 40% when the prior twin birth was before 30 weeks of gestation (35, 36).

Clinical factors during a current pregnancy that have been associated with an increased risk of preterm birth include vaginal bleeding, urinary tract infections (UTIs), genital tract infections, and periodontal disease (37). However, treatments for these potential risk factors have not been shown definitively to decrease the rate of preterm birth. Bacterial vaginosis is associated with a twofold increased risk of spontaneous preterm birth. The association between bacterial vaginosis and preterm birth is stronger when bacterial vaginosis is detected early in pregnancy. Despite the association, antibiotic treatment of bacterial vaginosis has not been consistently shown to reduce the risk of preterm birth (38). Early studies of the role of UTIs in preterm birth demonstrated an association between untreated asymptomatic bacteriuria in early pregnancy and increased rates of preterm birth (39, 40). However, subsequent treatment studies reported conflicting results, and a Cochrane review of 10 trials failed to find an association between treatment of symptomatic urinary infections and preterm birth (41). Thus, the association between treating UTIs in pregnancy and reducing preterm birth risk may be related mostly to preventing progression of asymptomatic bacteriuria to pyelonephritis (41, 42).

Observational studies suggest that women with periodontal disease have an increased risk of preterm birth (43, 44). However, treatment trials have yielded conflicting results, and two meta-analyses of randomized trials found no evidence that treatment of periodontal disease in pregnancy reduced the rate of preterm birth (45, 46), indicating that the risk may be due to associated factors rather than periodontal disease itself (47, 48).

A history of dilation and curettage (D&C) has been associated with an increased risk of preterm birth in some, but not all, studies. A meta-analysis of 21 studies including almost 2 million women found an association between subsequent preterm birth and history of D&C (odds ratio [OR], 1.29; 95% CI, 1.17–1.42), with slightly greater odds after multiple D&C procedures compared with no procedures (OR, 1.74; 95% CI, 1.10–2.76) (49). The mechanism of this association is uncertain, and intrauterine microbial colonization, endometrial injury, and other host and environmental factors have been suggested as contributors (50).

The preterm birth rate is much higher in multiple gestations than for singletons (51). Although the 2018 preterm birth rate for singleton pregnancies was 8.2%, for twins the overall preterm birth rate was 60.3%, with an early preterm birth (less than 34 completed weeks of gestation) rate of 19.5%. Triplets had a preterm birth rate of 98.3%, with 82.6% delivering in the early preterm period (6).

Before the widespread use of ultrasonography to assess the cervix, digital cervical examination was used to assess risk, and a soft cervix and a Bishop score of 4 or more in the second trimester were associated with an increased likelihood of preterm birth (17). Subsequently, a short cervical length as measured with endovaginal ultrasonography has been associated with an increased risk of preterm birth (52–54). Although many of the studies have used different definitions and different screening intervals, a *short cervical length* is most commonly defined as less than 25 mm, typically measured between 16 and 24 weeks of gestation. This 25 mm cutoff has been associated with an increased risk of preterm birth in a variety of screened populations (52, 55, 56). In general, shorter cervical lengths carry a greater risk of preterm birth.

Because of its effect on cervical length, surgical treatment of dysplasia with cold-knife conization, loop electrosurgical excision, or laser ablation also has been suggested as a risk factor for preterm birth (57). However, observational data in patients with a surgically shortened cervix have been inconsistent with regard to preterm birth risk, and factors other than anatomic cervical shortening

may be important in these patients (58–60). The risk of preterm birth may be increased among patients with excisions greater than 15 mm in depth (61) and short interval from excision to conception (62).

Strategies to Assess Risk of Preterm Birth

Assessment of cervical length in the second trimester has been shown to identify women at increased risk for preterm birth (55, 63). Endovaginal ultrasonography of the cervix provides an accurate and reproducible assessment of cervical length and, unlike transabdominal imaging, is not affected by maternal obesity, position of the cervix, or shadowing by the fetus (64–66).

Measurement of the cervix with endovaginal ultrasonography should be performed using a standardized method (67). With an empty maternal bladder, the endovaginal probe is placed in the anterior fornix without applying pressure to the cervix. The cervical length is measured by placing the calipers at either end of the echodense line between the external and internal cervical os, which represents the endocervical canal. Three measurements are taken, and the shortest is reported and used for assessment (52, 68). Cervical shortening earlier in the second trimester is more predictive of preterm delivery than shortening beyond 24 0/7 weeks of gestation (69). The presence of intraamniotic "debris" or "sludge" appears to be associated with additional risk of preterm birth in patients with a short cervix, but other findings, such as funneling of the internal os, change with fundal pressure, and change in length observed over serial examinations, do not appear to add appreciably to the predictive value of cervical length alone (70,71).

Although endovaginal sonography is the more accurate method of measuring cervical length in the second trimester, transabdominal ultrasonography has been investigated as an initial screen for short cervix (72, 73). In a prospective cohort study of 1,217 women who had transabdominal followed by endovaginal measurement of cervical length between 18 0/7 and 23 6/7 weeks of gestation, a transabdominal cervical length threshold of 36 mm or less identified 96% of patients with a cervical length of 25 mm or less on subsequent endovaginal imaging, and a transabdominal length of 35 mm or less identified 100% of patients with a cervical length of 20 mm or less on endovaginal ultrasonography (72). Using these cutoffs, the authors calculated that approximately 40% of patients in this series would have been able to avoid a separate endovaginal ultrasound procedure because their transabdominally measured length was above the threshold.

A variety of other tests and monitoring modalities have been proposed as markers for preterm delivery risk. The presence of fetal fibronectin in cervicovaginal secretions has been implicated as a risk factor for preterm birth. Although the absence of fetal fibronectin in women with preterm labor symptoms has a high negative predictive value for late preterm birth, the presence of fetal fibronectin has a low positive predictive value in asymptomatic women and, therefore, fetal fibronectin is not recommended as a primary screening test for preterm birth in asymptomatic women (56).

A number of multifactorial risk-scoring systems have been developed and tested to identify patients at risk for preterm birth based on history, physical findings, and social and economic risk factors (74). In general, these have performed poorly in clinical use (75, 76). Ongoing studies are evaluating the use of serum biomarkers, genital tract microbiome, salivary hormone and protein concentrations, cervical texture, and genetic profiling for preterm birth risk assessment (77–84).

Wireless technologies have enabled development of self-managed contraction monitors, which are marketed directly to patients. Home monitoring of uterine activity previously has been studied, and it has not been shown to reduce the risk of preterm birth (85). Until the efficacy, predictive values, and cost-effectiveness of these modalities and applications are clearer, these emerging prediction methods should be considered investigational, and routine adoption into clinical practice is not recommended.

Clinical Considerations and Recommendations

▶ ***Which patients should be screened with cervical sonography to assess their risk of preterm birth?***

Although prior preterm birth, prior PPROM, multiple gestation, and a short cervix are the strongest predictors of preterm birth, all pregnant women are at risk for preterm birth, and approximately 5% of nulliparous individuals will have a spontaneous preterm birth (56). To be effective, a screening program intended to identify women at highest risk for preterm birth needs to have an adequately high detection rate, an appropriately low false-positive rate, and an acceptable positive predictive value. Importantly, an effective treatment to reduce preterm birth should be available, and the screening program should be feasible, cost-effective, and accessible to all patients.

Table 1. Screening and Interventions for Prevention of Preterm Birth

Cervical length ultrasound	IM 17-OHPC	Vaginal progesterone	Ultrasound-indicated cerclage	Physical examination-indicated cerclage	Cervical pessary
Singleton pregnancy, no prior preterm birth					
Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment	Not indicated	Recommended for cervical length less than 25 mm	Insufficient data; possibly of benefit if the cervical length is less than 10 mm	Consider	Not indicated
Singleton pregnancy, prior spontaneous preterm birth					
Serial (every 1–4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation	Offer progesterone supplementation (either 17-OHPC or vaginal progesterone)	Offer progesterone supplementation (either 17-OHPC or vaginal progesterone) If not on progesterone already, consider with a cervical length less than 25 mm (versus cerclage)	Consider with a cervical length less than 25 mm (versus vaginal progesterone if not already on progesterone supplementation)	Consider	Not indicated
Multiple gestation					
Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment	Not indicated	Insufficient data	Insufficient data	Consider	Not indicated

Abbreviations: IM, intramuscular; 17-OHPC, 17-alpha hydroxyprogesterone caproate.

Patients With a Singleton Pregnancy with No Prior Spontaneous Preterm Delivery

Whether and how to screen nulliparous women and individuals without a history of preterm birth is a matter of uncertainty and debate. Because the risk of preterm birth is low in this group, it is difficult to show benefit from universal screening with either transabdominal or endovaginal ultrasonography. Also, the low incidence of short cervix in low-risk individuals limits the applicability of cervical length screening.

The efficacy of screening low-risk women with serial endovaginal ultrasonography of the cervix was assessed in a prospective cohort study of more than 9,400 nulliparous women with singleton pregnancies (56). Cervical length measurement was done twice, at medians of 19 and 28 weeks of gestation. Only 1% of women had a

cervical length less than 15 mm between 16 and 22 weeks of gestation, and the positive predictive value of a cervical length of 20 mm or less between 16 and 22 weeks of gestation was only 15.5%. The authors estimated that 680 women would need to be screened at a cutoff of 20 mm to predict one spontaneous preterm birth. Another prospective cohort study of more than 1,500 women without a prior spontaneous preterm birth who were followed with endovaginal ultrasonography found similar results, with 1.1% of women having a cervical length of 20 mm or less before 24 0/7 weeks of gestation and no difference in preterm birth rates between women who were screened and those who were not (86). In patients with a prior term delivery, the incidence of short cervix is even lower (87).

Decision analysis and cost-effectiveness analysis techniques also have been used to assess a policy of universal cervical length screening with endovaginal ultrasonography. Although some studies suggest a benefit to universal cervical length screening (88, 89), they have been criticized for using cost and treatment estimates that were overly optimistic (90). The matter remains unsettled, because two cost-effectiveness analyses using similar estimates of treatment efficacy came to opposite conclusions (91, 92).

Regardless of the uncertainty about the utility of universal endovaginal cervical length screening for the prevention of preterm birth, the cervix should be visualized as part of the 18 0/7–22 6/7 weeks of gestation anatomy assessment (93). If on transabdominal ultrasonography a short cervix is found or suspected, endovaginal ultrasonography is recommended to more accurately assess cervical length (94). The incidental finding of a short cervix is associated with an increased risk of preterm delivery in this group (56), and several randomized trials have shown that vaginal progesterone treatment reduces the risk of preterm birth in these patients (54, 95). Therefore**,** the cervix should be visualized at the 18 0/7–22 6/7 weeks of gestation anatomy assessment in individuals without a prior preterm birth, with either a transabdominal or endovaginal approach. Screening of cervical length with serial endovaginal ultrasonography is not indicated in pregnant individuals without a prior preterm birth.

Patients With a Singleton Pregnancy and a Prior Spontaneous Preterm Delivery

Women with a prior spontaneous preterm birth are at high risk for recurrent preterm birth (17, 33). Women who have an early spontaneous preterm birth for their first delivery have a second spontaneous preterm birth in their next pregnancy approximately 35% of the time (33). In these women with prior spontaneous preterm birth, a short cervix is clearly associated with an increased risk of preterm birth compared with women with a prior spontaneous preterm birth who have a normal cervical length (96–98).

A systematic review that included 14 articles estimated the ability of endovaginal ultrasound cervical length measurement to predict spontaneous preterm birth in women at high risk because of prior preterm birth, prior cervical loop electrosurgical excision or conization, or uterine anomaly (55). The authors found that a cervical length less than 25 mm before 24 weeks of gestation had a sensitivity of 65.4% for preterm birth before 35 weeks of gestation, with a positive predictive value of 33.0% and a negative predictive value of 92.0%. Sub-analysis of the studies that included only women whose risk factor was prior spontaneous preterm birth found a similar sensitivity and a positive predictive value of 41.4% (55).

Although most studies have assessed cervical length between 16 0/7 and 24 0/7 weeks of gestation, there are no satisfactory data to define the ideal timing and schedule of cervical length measurement for screening patients with prior preterm birth. Most guidelines do not specify timing or schedule (99,100), but a series of ultrasound measurements of cervical length beginning at around 16 0/7 weeks of gestation and repeated every 1–4 weeks until 24 0/7 weeks of gestation is consistent with most published study protocols (101).

Because of the relatively high detection rate and predictive value in individuals with prior preterm birth, and because treatment is available, serial endovaginal ultrasound measurement of cervical length beginning at 16 0/7 weeks of gestation and repeated until 24 0/7 weeks of gestation for individuals with a singleton pregnancy and a prior spontaneous preterm birth is recommended. Evidence regarding the benefits of clinical interventions to decrease the risk of preterm birth in patients with a shortened cervix and prior preterm birth is detailed in the clinical question on this topic below.

Patients With a Multiple Gestation

In twin pregnancies, a shortened cervix in the second trimester is more common than in singleton pregnancies, and a short cervix is a predictor of early preterm birth (11, 102–105). A systematic review and meta-analysis of 16 studies of asymptomatic women with twin pregnancies examined the accuracy of second-trimester ultrasound measurement of cervical length to predict preterm birth (106). All of the studies used endovaginal ultrasonography for screening and did not include any interventions. A cervical length of 25 mm or less at 20–24 weeks of gestation demonstrated a positive predictive value of 75.5% for delivery before 37 weeks of gestation and 25.8% for

delivery before 28 weeks of gestation. A shorter cervical length cutoff of 20 mm or less had a positive predictive value of 61.9% for delivery before 34 weeks of gestation.

Evidence regarding the uncertain benefits of clinical interventions to decrease the risk of preterm birth in patients with a multiple gestation and a shortened cervix is detailed in the clinical question on this topic below. Given that the effectiveness of interventions for a short cervix in a twin pregnancy are unclear, the data are insufficient to recommend for or against routine endovaginal ultrasound screening of cervical length in twin pregnancy. As with singleton pregnancies, the cervix should be visualized as part of the 18 0/7–22 6/7 weeks of gestation anatomy assessment (93). If on routine transabdominal ultrasonography a short cervix is found or suspected, endovaginal ultrasonography is recommended to more accurately assess cervical length (94).

There is a paucity of information about optimal cervical length screening and treatment approaches for individuals with higher-order multiple gestations.

Patients With a History of a Medically Indicated Preterm Delivery

Many preterm births, especially late preterm births, are medically indicated (107). Conditions that often warrant preterm delivery include preeclampsia with severe features, poorly controlled pregestational diabetes, placenta previa, and suspected growth restriction with abnormal antenatal testing or Doppler studies (107, 108).

An analysis of U.S. birth certificate data from 1989 to 1997 found that women with a medically indicated preterm birth before 35 weeks of gestation in their first pregnancy had 10 times higher odds of another preterm birth than women who had not (OR, 10.6; 95% CI, 9.1–12.4) (109). Similarly, a Danish study showed that the risk of preterm birth at less than 37 weeks of gestation in the second pregnancy was the same for women with either a spontaneous or medically indicated preterm birth in the first pregnancy (110).

A retrospective cohort study of more than 50,000 women confirmed the high likelihood for medically indicated preterm birth to repeat in consecutive pregnancies (111). A prior medically indicated preterm birth conferred a 9.1-fold increased risk for a subsequent indicated preterm birth (adjusted relative risk [RR], 9.10; 95% CI, 4.68–17.71). Also, a prior medically indicated preterm birth increased the risk of a spontaneous preterm birth in the next pregnancy (adjusted RR, 2.7; 95% CI, 2.00–3.65).

Although there appears to be an increased risk of spontaneous preterm birth in individuals with a prior medically indicated preterm birth, there is insufficient evidence to support a recommendation that these individuals undergo serial cervical length surveillance in future pregnancies. Attempting to reduce the risk of a recurrent indicated preterm birth is recommended, with prepregnancy control of any underlying medical condition and close medical management and fetal surveillance during pregnancy, including the use of low-dose aspirin for reduction of the risk of preeclampsia in patients at high risk for preeclampsia (112).

▶ *Should patients undergo screening for bacterial vaginosis during pregnancy for the purpose of preventing preterm birth?*

Bacterial vaginosis has been associated with preterm birth in some reports, but interventional studies of screening and treatment of asymptomatic women have not shown a reduction in preterm birth rates (113). A Cochrane meta-analysis of 21 trials involving 7,847 pregnant women with bacterial vaginosis detected through screening was performed. Although antibiotic therapy was highly effective in eradicating bacterial vaginosis, it did not reduce the risk of preterm birth at less than 37 weeks of gestation (OR, 0.88; 95% CI, 0.71–1.09) (38).

Prophylactic antibiotics for the prevention of preterm birth also have been investigated. In a meta-analysis of 8 trials assessing the use of prophylactic antibiotics in the second or third trimester of pregnancy to reduce adverse pregnancy outcomes, antibiotic treatment reduced preterm delivery compared with no treatment only in the subgroup of women with a prior preterm birth and current bacterial vaginosis (RR, 0.64; 95% CI, 0.47–0.88; one trial, 258 women) (114). For the purpose of prevention of preterm birth, screening and antibiotic treatment for bacterial vaginosis in pregnant individuals without symptoms of vaginitis is not recommended. Although there may be benefits to early screening and treatment of bacterial vaginosis in asymptomatic pregnant women who have a history of a previous preterm delivery, there are insufficient data to recommend this as a routine practice in this population (115).

▶ *What interventions reduce the risk of preterm birth in patients with a short cervix, singleton pregnancy, and no history of preterm birth?*

Vaginal Progesterone

Vaginal progesterone has been studied extensively as a treatment to reduce the risk of preterm birth in asymptomatic women with a singleton pregnancy, short cervix, and no prior preterm birth. One trial randomized 250 women (212 with no prior preterm birth) with a cervical length of 15 mm or less between 20 and 25 weeks of gestation to receive vaginal suppositories of either 200 mg micronized progesterone or placebo (95). Treatment with progesterone decreased preterm delivery

before 34 weeks of gestation (19.2% versus 34.4%; RR, 0.56; 95% CI, 0.36–0.86).

In another randomized trial, 458 asymptomatic patients with a singleton gestation, no prior preterm birth, and a cervical length of 10–20 mm, received either daily vaginal application of 90 mg progesterone gel or placebo beginning between 20 0/7 and 23 6/7 weeks of gestation (54). Patients who received vaginal progesterone had a lower incidence of delivery before 33 weeks of gestation (7.6% versus 15.3%; adjusted RR, 0.50; 95% CI, 0.27–0.90; $P=.02$). For the entire study group (including 59 additional patients with a prior preterm birth), the authors calculated that 14 women with a short cervix would need to be treated to prevent one preterm birth before 33 weeks of gestation, and 22 women would need treatment to prevent one case of neonatal respiratory distress (54). Another randomized trial compared daily vaginal 200 mg progesterone soft capsules to placebo initiated between 22 and 24 weeks of gestation and continued until 34 weeks in a heterogenous group of women with a mixture of risk factors for preterm birth, including a cervical length of 25 mm or less between 18 0/7 and 24 0/7 weeks of gestation (116). In contrast to the other trials that focused specifically on patients with a short cervix, the authors found no difference in neonatal morbidities, childhood development, or fetal death or preterm birth before 34 0/7 weeks of gestation.

Subsequently, a meta-analysis of five randomized trials of vaginal progesterone versus placebo in patients with a singleton pregnancy, a short cervix, and no prior preterm birth was performed, including patients from the 2019 OPPTIMUM (Does Progesterone Prophylaxis to Prevent Preterm Labour Improve Outcome?) trial who did not have other risk factors, and standardizing the threshold definition of shortened cervix at 25 mm or less for their analysis (116, 117). Patients treated with vaginal progesterone had a significantly reduced risk of any preterm birth before 34 0/7 weeks of gestation (14.5% versus 24.6%; RR, 0.60; 95% CI, 0.44–0.82), spontaneous preterm birth before 34 0/7 weeks of gestation (RR, 0.63; 95% CI, 0.44–0.88), neonatal respiratory distress, and neonatal intensive care unit admission. The meta-analysis authors calculated that 14 patients would need to be treated to prevent one spontaneous preterm birth before 34 0/7 weeks of gestation (117). A meta-analysis of the same trials but using individual patient data confirmed the benefit of vaginal progesterone in patients with a singleton gestation and cervical length of 25 mm or less (118). A subsequent individual patient data meta-analysis including 31 trials of progesterone (vaginal, intramuscular, or oral) for women an increased risk of preterm delivery due to a short cervix or a history of preterm birth also found evidence for a reduction in risk of preterm birth in singleton pregnancies with vaginal progesterone compared to untreated controls (RR, 0.78; 95% CI, 0.68–0.90). In this meta-analysis, among women with no prior preterm birth and cervical length of 25 mm or less, the fixed effects model indicated that the relative risk for preterm birth before 34 weeks of gestation was 0.69 (95% CI, 0.48–0.98). The authors concluded that treatment might be most useful in people with short cervical lengths as this population is at the highest a priori risk of preterm birth, resulting in a greater absolute risk reduction with treatment (119).

Because of the consistency of these results, vaginal progesterone is recommended for asymptomatic individuals without a history of preterm birth with a singleton pregnancy and a short cervix. Although most studies used 200 mg progesterone daily from the time of identification of a cervix shorter than 25 mm at 18 0/7–25 6/7 weeks of gestation until 36–37 weeks of gestation, there are no adequate dosing studies or comparative trials, and there are insufficient data to indicate which formulation and which dose are most effective.

Intramuscular Progesterone

There are few studies that assess alternatives to vaginal progesterone such as other routes of administration or other progestins for prevention of preterm delivery in patients with a short cervix in the second trimester. One open-label randomized trial compared weekly intramuscular injections of 500 mg 17-alpha hydroxyprogesterone caproate (17-OHPC) to no treatment in 105 women with cervical length of less than 25 mm (120). Although there were no differences in maternal or neonatal outcomes, their protocol included women with multiple risk factors for preterm birth; more than half had a prior preterm birth, and enrollment was allowed up to 31 6/7 weeks of gestation. One trial randomized patients with a cervical length less than 25 mm between 16 and 24 weeks of gestation to receive either 250 mg 17-OHPC or 400 mg vaginal progesterone suppositories (121). They found no difference in the rate of preterm birth before 34 weeks of gestation (4.8% with vaginal progesterone versus 4.7% with 17-OHPC).

Additional evidence comes from a randomized blinded trial of 657 nulliparous women with a cervical length of less than 30 mm between 16 0/7 and 22 3/7 weeks of gestation (122). Patients received weekly intramuscular injections of either 250 mg 17-OHPC or placebo. There was no difference between the groups with regard to delivery before 35 0/7 weeks of gestation (13.5% versus 16.1%; RR, 0.84; 95% CI, 0.58–1.21), delivery before 32 0/7 weeks of gestation (8.6% versus 9.7%; RR, 0.88; 95% CI, 0.54–1.43), or composite

neonatal morbidity (7.0% versus 9.1%; RR, 0.77; 95% CI, 0.46–1.30). A subsequent individual patient data meta-analysis including 31 trials of progesterone in asymptomatic women at risk for preterm birth due to prior preterm birth or short cervix concluded that the evidence for reduction of risk of preterm birth was most certain for vaginal progesterone, although there was no clear evidence that either formulation was superior (119). Thus, vaginal progesterone has the most consistent evidence for preventing preterm birth associated with a short cervix in individuals without a history of spontaneous preterm birth. Intramuscular 17-OHPC is not recommended for prevention of preterm birth in patients who do not have a history of spontaneous preterm delivery.

Cervical Cerclage

Ultrasound-Indicated Cerclage

Cerclage has been assessed in five randomized trials that enrolled patients with a short cervical length in the second trimester (123–127). None of the patients received vaginal progesterone, and although no significant difference in preterm birth was found in any of the trials, all were relatively small. A meta-analysis of those trials and using individual data from the 419 patients without a prior preterm birth was performed (128). In patients with a cervical length less than 25 mm, cerclage did not decrease the risk of preterm birth before 37 0/7 weeks of gestation (36.2% versus 41.0%; RR, 0.93; 95% CI, 0.73–1.18), preterm birth before 34 0/7 weeks of gestation (20.1% versus 25.1%; RR, 0.89; 95% CI, 0.63–1.27), or any of the neonatal morbidities that were assessed. However, in a planned subgroup analysis of the 126 patients with a cervical length of less than 10 mm, patients who received cerclage had a lower risk of delivery before 35 0/7 weeks of gestation (39.5% versus 58.0%; RR, 0.68; 95% CI, 0.47–0.98). Although the risk of bias in the studies was not high, their overall quality of evidence was considered to be low because of small cohorts and imprecision. Cervical cerclage is of uncertain effectiveness in patients with a short cervix and no history of preterm birth. However, there is evidence of potential benefit in patients with a very short cervical length.

Examination-Indicated Cerclage

Individuals with cervical insufficiency based on a dilated cervix on a digital or speculum examination at 16 0/7–23 6/7 weeks of gestation are candidates for a physical examination-indicated cerclage. A meta-analysis that included a randomized controlled trial, two prospective cohort studies, and seven retrospective cohort studies found that cerclage was associated with prolongation of pregnancy (mean difference, 33.98 days; 95% CI, 17.88–50.08 days) and increased neonatal survival (71% versus 43%; RR, 1.65; 95% CI, 1.19–2.28) (129). The strength of this conclusion is limited by the potential for bias in the included studies. Maternal and operative complications including cervical laceration, intraoperative rupture of membranes, and sepsis were reported inconsistently and variably in the included studies.

Amniocentesis to assess for infection is offered by some physicians before the performance of examination-indicated cerclage. A retrospective cohort of all patients who underwent either an examination- or ultrasound-indicated cerclage included a total of 160 patients who underwent a cerclage (130). Sixty-five patients who had an amniocentesis performed before the cerclage were compared with 95 patients who underwent a cerclage without an amniocentesis. None of the amniocentesis results were positive for infection in those patients that received a cerclage. Patients that had an amniocentesis before cerclage were found to have an earlier gestational age at the time of the procedure (20.30 ± 2.29 weeks versus 21.32 ± 1.81 weeks, $P<.001$), a shorter cervical length on presentation (0.93 ± 0.61 cm versus 1.45 ± 0.66 cm, $P<.001$), a delivery at an earlier gestational age (gestational age 32.2 [30.3–34.2] versus 36.3 [35.2–37.3] weeks of gestation, $P<.001$) with shorter time from cerclage placement until delivery (gestational age 13.9 [0.0–24.0] versus 16.3 [0.3–23.2] weeks of gestation, $P=.010$). The rates of chorioamnionitis and PPROM were significantly higher in the amniocentesis group (chorioamnionitis: 17% versus 2%, $P=.0008$; PPROM: 26% versus 13%, $P=.03$). The severity of presentation was the determining factor in the decision to perform an amniocentesis before cerclage placement and, because of this difference in severity, outcomes for the amniocentesis group were predictably worse than those who did not undergo amniocentesis (130). It is uncertain whether performance of amniocentesis before offering examination-indicated cerclage influences anticipated outcomes.

With respect to additional therapeutic approaches along with examination-indicated cerclage, a randomized trial investigated perioperative indomethacin and antibiotics or no perioperative prophylactic medications among individuals with a singleton pregnancy between 16 0/7 and 23 6/7 weeks of gestation undergoing an examination-indicated cerclage (131). A greater proportion of pregnancies were prolonged by at least 28 days among women who received indomethacin and perioperative antibiotics (24 [92.3%] versus 15 [62.5%]; $P=.01$). However, gestational age at delivery and neonatal outcomes were statistically similar between groups. A subsequent retrospective cohort study from the same institution reported similar

findings (132). A systematic review did not identify any additional data to inform the use of additional therapies along with cerclage (133).

Examination-indicated cerclage may be of benefit in an appropriately selected candidate; however, the data regarding the optimal selection criteria are unclear. In counseling of individuals with a dilated cervix in the second trimester who are considering a cerclage, in addition to discussing the maternal risks and potential neonatal benefits, it is important to note that although there may be an extension of the pregnancy, it may extend the pregnancy just to periviability or just past viability, committing the pregnancy to an early preterm birth as opposed to a pregnancy loss. As individuals' preferences for these outcomes can vary, a conversation about these potential outcomes is critical in facilitating shared medical decision making. Contraindications are clinical scenarios in which cerclage would represent a significant threat to maternal health or in which benefit is not anticipated: fetal demise, fetal anomaly incompatible with life, intrauterine infection, active bleeding, active preterm labor, and PPROM.

Pessary

Vaginal pessaries, commonly used to treat genital prolapse, also have been evaluated for prevention of preterm birth. Most commonly, a cervical pessary that encircles, compresses, elevates, and posteriorly rotates the cervix has been used (134).

A meta-analysis of three randomized trials including 1,420 patients with a singleton pregnancy and a cervical length of 25 mm or less compared cervical pessary with routine care. Approximately 14% of study patients had a prior preterm birth, and in one trial patients with a cervical length of 15 mm or less also received vaginal progesterone. Treatment with the cervical pessary did not decrease the risk of spontaneous preterm delivery before 34 0/7 weeks of gestation (10.2% versus 14.6%; RR, 0.71; 95% CI, 0.21–2.42), neonatal intensive care unit admission, or other neonatal morbidities (135). Subsequently, a randomized trial of 300 patients with no prior preterm birth and with a cervical length of 25 mm or less between 18 0/7 and 23 6/7 weeks of gestation found a lower rate of spontaneous preterm birth before 34 weeks of gestation (7.3% vs 15.3%; RR, 0.48; 95% CI, 0.24–0.95), lower rates of neonatal intensive care unit admission, and lower composite neonatal morbidity with pessary use (136). Lastly, a randomized trial of cervical pessary compared with routine care included 122 women with a singleton pregnancy, a cervical length of 25 mm or less, and no history of spontaneous preterm birth and found no differences in preterm birth or adverse neonatal outcomes (137).

A meta-analysis of 12 randomized controlled trials (4,687 women and 7,167 fetuses/infants) compared cervical pessary with standard care (no pessary) or alternative interventions in asymptomatic women at high risk for preterm birth (138). There were no significant differences between the pessary and no-pessary groups in the risk of spontaneous preterm birth before 34 weeks of gestation among singleton gestations with a cervical length 25 mm or less (RR, 0.80; 95% CI, 0.43–1.49; 6 trials, 1,982 women; low-quality evidence). No significant differences were observed between the pessary and no-pessary groups in preterm birth before 37, 32, and 28 weeks of gestation and in most adverse pregnancy, maternal, and perinatal outcomes (low- to moderate-quality evidence for most outcomes).

The cervical pessary also has been studied in combination with vaginal progesterone. In a randomized trial of 144 women with a singleton pregnancy and a cervical length of 25 mm or less between 18 and 22 weeks of gestation, patients received either vaginal progesterone 400 mg daily or vaginal progesterone plus a cervical pessary (139). There were no differences in preterm birth before 34 weeks of gestation (9.6% versus 14.0%) or neonatal morbidity. In another study, patients at risk for preterm birth were randomized to receive either a cervical pessary alone or the pessary and daily treatment with 200 mg progesterone vaginal suppositories (140). Data from the subset of 51 patients with no history of preterm birth but with a short cervix (defined as being below the third percentile for gestational age) showed no difference in preterm birth before 34 weeks of gestation with addition of progesterone (28.0% versus 26.9%; $P=.84$).

Taken together, these data strongly suggest that the cervical pessary is ineffective for prevention of preterm birth in patients with a short cervix, singleton pregnancy, and no history of preterm birth. Cervical pessary is not recommended for the singleton pregnancy with a short cervix and no history of spontaneous preterm birth.

▶ ***How should the current pregnancy be managed in a patient with a prior spontaneous preterm delivery?***

Progesterone Supplementation

Preterm birth prophylaxis with progesterone has been studied since the 1960s, with many reports showing a benefit. An early meta-analysis of trials using 17-OHPC suggested a reduction in preterm birth with progestogen treatment (141), eventually leading to a multicenter trial

involving patients with a singleton pregnancy and a prior preterm birth (142). Four hundred sixty-three patients were randomized to weekly intramuscular injections of either 250 mg 17-OHPC or placebo, starting between 16 0/7 and 20 6/7 weeks of gestation. Administration of 17-OHPC reduced the rate of preterm birth before 35 weeks of gestation by one third (20.6% versus 30.7%; RR, 0.67; 95% CI, 0.48–0.93). In addition to the clinical benefit, cost-effectiveness analyses calculated an economic benefit for use of 17-OHPC in patients with a prior preterm birth (143, 144). Administration of 17-OHPC was then broadly recommended for all patients with a prior preterm birth by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine in 2003.

Although some groups had similar results when 17-OHPC was put into clinical practice (145), some subsequent studies have not shown benefit with 17-OHPC. A prospective cohort study of 430 women with a prior delivery at or before 35 weeks of gestation did not find a significant reduction in preterm birth with 17-OHPC treatment, compared with historical controls (146). The post-marketing follow-up trial (PROLONG) evaluated the efficacy of 17-OHPC 250 mg intramuscular injection weekly compared with placebo on preterm birth and neonatal morbidity among women with a singleton pregnancy and prior spontaneous preterm birth (147). The study was a large international multicenter, randomized, controlled, double-blind trial conducted from November 2009 to October 2018 that evaluated 1,877 eligible women, of which 1,740 provided informed consent and underwent randomization. This study demonstrated no statistical difference in the two primary outcomes of preterm birth before 35 0/7 weeks of gestation (11.0% versus 11.5%; RR, 0.95; 95% CI, 0.71–1.26; $P=.72$) and neonatal composite index (5.6% versus 5.0%; RR, 1.12; 95% CI, 0.70–1.66; $P=.73$). No differences were detected in other perinatal or maternal outcomes as well.

Vaginal progesterone also has been studied for the indication of prior preterm birth. Meta-analyses of the three randomized trials comparing intramuscular 17-OHPC to vaginal progesterone found that patients who received vaginal progesterone had a lower risk of preterm birth before 34 weeks of gestation than women who received 17-OHPC (17.5% versus 25.0%; RR, 0.71; 95% CI, 0.53–0.95) (148, 149). The three trials used different doses of vaginal progesterone and were not blinded but excluded patients with a short cervix (150–152). Three blinded trials of vaginal progesterone versus placebo, using differing doses and preparations starting at 18–22 weeks of gestation, have shown no benefit in reducing recurrent preterm birth (116, 153, 154).

A systematic review and network meta-analysis including 40 trials of women with singleton pregnancies at risk for preterm birth concluded that both vaginal progesterone and 17-OHPC were effective at reducing the risk for recurrent preterm birth, although the evidence was most robust for vaginal progesterone (preterm birth before 34 weeks of gestation, OR, 0.29; 95% credibility interval, 0.12–0.68) compared with 17-OHPC (preterm birth before 37 weeks of gestation, OR, 0.53; 95% credibility interval, 0.27–0.95) (155). A subsequent individual patient data meta-analysis including 31 trials of progesterone in asymptomatic women at risk for preterm birth due to prior preterm birth or short cervix, including the PROLONG study, found evidence for a reduction in the risk of preterm birth before 34 weeks with progesterone treatment compared with control (vaginal progesterone, RR, 0.78; 95% CI, 0.68–0.90; 17-OHPC, RR, 0.83; 95% CI, 0.68–1.01) (119). Although the findings for 17-OHPC compared with control did not reach statistical significance, the authors concluded that there was not clear evidence of a difference in effect of progesterone based on indication for treatment or route of administration. The authors acknowledge that there was little evidence comparing vaginal progesterone and 17-OHPC directly. The most consistent evidence was for vaginal progesterone, and the authors concluded that due to the increased underlying risk of preterm birth, the absolute risk reduction was greatest for women with a short cervix and, therefore, treatment might be most useful for these patients. Compared to placebo, no significant increase in composite maternal complications was observed for 17-OHPC (RR, 1.18; 95% CI, 0.97–1.43) and vaginal progesterone (RR, 1.14; 95% CI, 0.93–1.40), and no maternal deaths were noted in any trials. These findings were based on limited data, because not all trials contributed data for maternal complications.

Consideration of progesterone supplementation for individuals at risk of recurrent preterm birth should continue to account for the body of evidence for progesterone supplementation, the values and preferences of the pregnant individual, the resources available, and the practicalities of the intervention. There are ongoing trials directly comparing vaginal progesterone with 17-OHPC, and this guidance will be updated as additional data become available. Patients with a singleton pregnancy and a prior spontaneous preterm birth should be offered progesterone supplementation (either vaginal or intramuscular) in the context of a shared decision-making process incorporating the available evidence and the patient's preferences. It appears that starting 17-OHPC earlier in the 16 0/7–20 6/7 weeks of gestation period is more effective than starting later (156). Early cessation of

17-OHPC has been associated with an increased risk of recurrent preterm birth (157).

Before 2011, all 17-OHPC (including that used in the 2003 trial) was produced in local and regional compounding pharmacies, because there was no 17-OHPC product approved by the U.S. Food and Drug Administration (FDA). In 2011, an intramuscular 17-OHPC formulation (Makena) was approved by the FDA for prevention of preterm birth, and a generic preparation of preservative-free 17-OHPC for intramuscular use also has been approved by the FDA (158). In 2018, a version of 17-OHPC for weekly subcutaneous injection was approved by the FDA. Because 17-OHPC was already approved for intramuscular use, FDA approval of the subcutaneous preparation did not require pharmacokinetic and efficacy studies in pregnant women, and approval was based on demonstration of similar blood levels and pharmacokinetics in postmenopausal subjects (159). Although the pharmacokinetic data are reassuring, there are no clinical data on which to make a recommendation regarding use of subcutaneous 17-OHPC in pregnant individuals at risk for preterm birth.

Cervical Length Monitoring and Subsequent Intervention

A short cervix in the second trimester is a strong predictor of preterm birth in patients with a prior preterm delivery (55, 96, 98, 160), and the two risk factors are additive (161). Because of this, serial endovaginal ultrasound monitoring of cervical length is recommended for all patients with a prior preterm birth (99–101). As mentioned previously, there are no adequate data to define the optimal timing and frequency of assessment, but cervical length measurements are usually initiated at about 16 0/7 weeks of gestation and repeated every 1–4 weeks, depending on individual patient risks and findings, until 24 0/7 weeks of gestation. If ultrasound monitoring detects a cervical length of 25 mm or less, options for intervention include cerclage or vaginal progesterone.

A meta-analysis of four randomized trials of cerclage found no benefit in women with a short cervix on second-trimester ultrasonography, but subanalysis using patient-level data identified a decrease in preterm birth before 35 weeks of gestation in those patients with a singleton pregnancy and prior preterm birth (RR, 0.61; 95% CI, 0.40–0.92) (162). Later, a randomized trial of 302 women with a prior spontaneous preterm birth and a second-trimester cervical length of less than 25 mm found no overall difference in preterm delivery before 35 weeks with cerclage. However, the planned sub-analysis of patients with cervical length of less than 15 mm found that cerclage significantly decreased preterm birth before 35 0/7 weeks (OR, 0.23; 95% CI, 0.08–0.66; $P=.006$) (163). A subsequent meta-analysis including all five trials, each of which provides weak evidence individually, found that in people with previous spontaneous preterm birth and cervical length of less than 25 mm before 24 weeks of gestation, cerclage reduced the rate of preterm birth before 35 weeks (28% versus 41%; RR, 0.70; 95% CI, 0.55–0.89) and composite neonatal morbidity (15.6% versus 24.8%; RR, 0.64; 95% CI, 0.45–0.91) (164). In patients who do receive a cerclage, further ultrasound monitoring of cervical length does not appear to be beneficial (101).

As previously discussed, treatment with vaginal progesterone has been shown to decrease the risk of preterm birth in patients with a short cervix without a prior preterm delivery. A meta-analysis of individual patient data from five randomized blinded trials of vaginal progesterone for a short second-trimester cervix demonstrated a decreased risk of preterm birth in the 288 included patients with a history of preterm birth (RR, 0.59; 95% CI, 0.40–0.88) (118). Few if any of the patients in these trials were receiving 17-OHPC to prevent recurrent preterm birth. Thus, although it is recommended that patients with a prior preterm delivery who develop a short cervix continue their 17-OHPC injections, and although vaginal progesterone appears to have benefit in these patients who are not receiving 17-OHPC, it is unknown what the interactions might be and whether there are additive (or negative) effects from combined progestogen treatment. There are not adequate data on which to make a recommendation regarding the addition of vaginal progesterone, or changing from intramuscular to vaginal progesterone, in patients who are receiving 17-OHPC and are found to have a short cervix on second-trimester screening.

There are no adequate trials directly comparing cerclage to vaginal progesterone in patients with a prior spontaneous preterm birth and a short cervix in the second trimester. However, trials of vaginal progesterone have shown similar benefits to those of cerclage in these patients. A meta-analysis compared the five randomized trials of vaginal progesterone versus placebo and the five randomized trials of cerclage versus no cerclage in women with a prior preterm birth and a short cervix before 24 weeks (165). The relative risk of preterm birth before 35 weeks was 0.68 (95% CI, 0.50–0.93) with vaginal progesterone and 0.70 (95% CI, 0.55–0.89) with cerclage. The composite neonatal morbidity–mortality outcome also was similar for the two treatments (vaginal progesterone: RR, 0.43; 95% CI, 0.20–0.94; cerclage: RR, 0.64; 95% CI, 0.45–0.91). Indirect comparison analysis found no difference between the two treatments.

Recognizing that most of these data are from patients who were not receiving 17-OHPC, it appears that

cerclage and vaginal progesterone are both effective for patients with a singleton pregnancy and a history of a preterm birth who also have a short cervix. Although some recommendations (164, 166) specify that cerclage should be offered to patients with a short second-trimester cervix and a prior preterm birth, vaginal progesterone is an acceptable option for these patients as well (165, 167). Thus, patients with a singleton gestation, a prior spontaneous preterm birth, and a short cervix in the second trimester who are not on progesterone supplementation should be informed of their increased risk of preterm birth, the two treatment options available (vaginal progesterone and cerclage), and the uncertainty about which management course is best in the context of a shared decision-making process. Patients with a singleton gestation, prior spontaneous preterm birth, and a short second-trimester cervix who are on progesterone supplementation should be informed of their increased risk of preterm birth, and cerclage may be offered in addition to continuation of progesterone.

▶ ***Does cerclage placement, cervical pessary, or progesterone treatment decrease the risk of preterm birth in patients with multiple gestations?***

Because of the high incidence of preterm birth in multiple gestations, a number of preventive treatments have been studied in unselected groups of asymptomatic patients with multiple gestation, including intramuscular 17-OHPC, vaginal progesterone, cerclage, and pessary.

Progesterone Treatment

Intramuscular Progesterone

A prospective trial of 17-OHPC in 661 twin pregnancies randomized patients to receive either 250 mg 17-OHPC or placebo at 16 0/7–20 6/7 weeks of gestation (168). There was no difference in delivery before 35 weeks of gestation or fetal death, or in their composite neonatal morbidity outcome. Subsequently, a Cochrane review of randomized trials of intramuscular progesterone versus placebo in twin pregnancy found a slight increase in the risk of preterm birth before 34 weeks of gestation with 17-OHPC (RR, 1.54; 95% CI, 1.06–2.26) and an increased risk of admission to the neonatal intensive care unit (RR, 1.33; 95% CI, 1.13–1.58), but no difference in perinatal mortality, respiratory distress syndrome, or most of the other neonatal morbidities (169). An individual patient meta-analysis also found no evidence of benefit for treatment in multiple gestations without other risk factors (twins or triplets, eight trials, 2,253 women: RR, 1.04; 95% CI, 0.92–1.18) (119). Intramuscular 17-OHPC is not recommended for prevention of preterm birth based solely on the indication of multiple gestation.

Among women with twin pregnancy and a prior spontaneous preterm birth, the effectiveness of 17-OHPC also has been examined (170). The rates of recurrent spontaneous preterm birth in twin pregnancies that had a prior singleton preterm birth were calculated in a study that used individual patient-level data from two prospective randomized placebo-controlled trials of prophylactic 17-OHPC in dichorionic/diamniotic twin gestation. Among 66 subjects, spontaneous delivery before 34 weeks of gestation occurred significantly less often in those randomized to 17-OHPC than in those randomized to placebo (20.6% versus 46.9%; $P=.03$). However, mean gestational length was not noticeably different, and there was no statistically significant difference in composite neonatal outcome. These data suggest that 17-OHPC may be beneficial to individuals with a prior preterm birth and a current dichorionic twin gestation.

Higher-Order Multiple Gestations

A meta-analysis of three randomized controlled trials of 17-OHPC versus placebo included 232 mothers with triplet pregnancies and their 696 offspring (171). The rate of the composite adverse perinatal outcome was similar among those treated with 17-OHPC and those treated with placebo (34% versus 35%; RR, 0.98; 95% CI, 0.74–1.3). The rate of birth before 32 weeks of gestation also was similar in the two groups (35% versus 38%; RR, 0.92; 95% CI, 0.55–1.56). It does not appear that prophylactic 17-OHPC given to patients with triplet pregnancies had any significant impact on perinatal outcome or pregnancy duration.

Vaginal Progesterone

Vaginal progesterone also has been studied in unselected twin pregnancies. As with singleton pregnancies, several different doses and formulations have been used. Two meta-analyses reviewed the cumulative experience in randomized clinical trials (169, 172). A Cochrane review of randomized trials of vaginal progesterone versus placebo in twin pregnancies found no difference in preterm birth before 34 weeks of gestation (RR, 0.83; 95% CI, 0.63–1.09), perinatal death (RR, 1.23; 95% CI, 0.74–2.06), neonatal intensive care unit admission (RR, 0.93; 95% CI, 0.87–1.00), or respiratory distress in the newborn (RR, 0.84; 95% CI, 0.64–1.10) (169). Two other meta-analyses using patient-level data showed similar results: vaginal progesterone did not reduce preterm birth before 35 weeks of gestation (RR, 0.94; 95% CI, 0.80–1.1), perinatal death (RR, 0.97; 95% CI, 0.65–1.4), or adverse neonatal outcome (RR, 0.97; 95% CI, 0.77–1.2) (172), nor did it reduce risk of preterm birth before 34 weeks of gestation (twins, eight trials, 2,046 women: RR, 1.01; 95% CI, 0.84–1.20) (119). A subsequent

double blind randomized controlled trial of vaginal progesterone 300 mg twice a day starting at 11–14 weeks versus placebo in 1,194 women with twin pregnancies showed no benefit for reduction of spontaneous preterm birth before 34 weeks of gestation (10.4% versus 8.2%; adjusted OR [aOR], 1.35; 95% CI, 0.88–2.05) (173). Routine prophylactic use of vaginal progesterone to prevent preterm birth in twin pregnancies is not recommended.

Because of its demonstrated benefit in singleton pregnancies with a short cervix, treatment with vaginal progesterone has been applied to individuals with asymptomatic twin pregnancies with a short cervix. Six randomized controlled trials have been published (95, 174–178). Again, different progesterone compounds and different doses were used, and most of the trials were too small to provide a valid conclusion. A meta-analysis using individual patient data was performed using those six trials (179). A total of 303 women with multiple gestations and a cervical length of 25 mm or less at randomization were included; 17.6% of those receiving placebo and 19.4% of those receiving vaginal progesterone had a history of preterm birth. Overall, the data were considered to be of moderate quality, although 74% of patients in the meta-analysis came from one study that was unblinded and at high risk for performance and detection bias. The meta-analysis showed that treatment with vaginal progesterone reduced the risk of preterm birth before 33 0/7 weeks of gestation (31.4% versus 43.1%; RR, 0.69; 95% CI, 0.51–0.93; $P=.01$). Similar reductions were seen in preterm birth at 34 weeks and in perinatal death, respiratory distress syndrome, and need for mechanical ventilation. However, a subsequent systematic review and network meta-analysis found no benefit for vaginal progesterone for unselected twin pregnancies or twin pregnancies with a short cervix (180). Although vaginal progesterone is a low-risk treatment, the data are of such quality to make definitive recommendations difficult in twin pregnancies with a short cervix.

Cerclage

Prophylactic Cerclage

Cervical cerclage has been studied in at least five randomized clinical trials that included unselected twin pregnancies (123, 124, 126, 181, 182). A Cochrane review analyzed the cumulative results and found no benefit to cerclage with regard to delivery before 34 weeks of gestation (46.2% with cerclage versus 31.8% without; RR, 1.16; 95% CI, 0.44–3.06), perinatal death (19.2% versus 9.5%; RR, 1.74; 95% CI, 0.92–3.28), or serious neonatal morbidity (15.8% versus 13.6%; RR, 0.96; 95% CI, 0.13–7.10) (183). Although the total number of patients analyzed from these trials is not large, and the confidence intervals are relatively wide, there is no evidence of benefit for prophylactic cerclage in unselected twin pregnancies. Cervical cerclage is not recommended for prevention of preterm birth based solely on the indication of multiple gestation.

Ultrasound-Indicated Cerclage

Cervical cerclage has been used in an effort to prevent preterm birth in twin pregnancy with a short cervix. Most of the published experience is composed of retrospective reports with a high risk of selection and treatment bias, involving nonrandomized patients compared with contemporary controls. One study reviewed the experience in four centers over 18 years (184). There were 140 women with an asymptomatic twin pregnancy and a cervical length of 25 mm or less between 16 and 24 weeks of gestation; 57 received a cerclage and 83 did not. There was no benefit to ultrasound-indicated cerclage with respect to spontaneous preterm birth before 34 weeks of gestation (29/57 [50.9%] versus 53/83 [63.9%]; aOR, 0.37; 95% CI, 0.16–1.1). However, the authors also analyzed their data from patients with a very short cervical length (15 mm or less) and found that cerclage decreased preterm birth before 34 weeks of gestation (16/32 [50%] versus 31/39 [79.5%]; aOR, 0.51; 95% CI, 0.31–0.83) and decreased neonatal care unit admissions among liveborn neonates (38/58 [65.5%] versus 63/76 [82.9%]; aOR, 0.42; 95% CI, 0.24–0.81). A systematic review and meta-analysis incorporating this and other cohort studies indicated a potential benefit for ultrasound-indicated cerclage in twin pregnancies with a cervical length shorter than 15 mm with a reduction in preterm birth before 34 weeks of gestation (83/216 versus 114/206 in the control group; RR, 0.73; 95% CI, 0.59–0.90) (185).

Three prospective randomized trials of cerclage that included twin pregnancies with a short cervix in the second trimester have been reported, totaling only 49 patients with twins (186). Individually, none of the studies showed benefit to cerclage, and one indicated an increased risk of preterm birth with cerclage (123). A meta-analysis of these randomized trials used individual patient-level data and adjusted for confounding variables, such as prior preterm birth (186). The analysis found that cerclage did not reduce the risk of preterm birth before 34 weeks of gestation (62.5% with cerclage versus 24.0% without; aOR, 1.17; 95% CI, 0.23–3.79). Birth weight less than 1,500 grams was increased in the cerclage group (52.1% versus 14.0%, aOR, 2.22; 95% CI, 1.07–5.73), as was respiratory distress syndrome (31.3% versus 6.0%; aOR, 3.88; 95% CI, 1.09–21.03). Analysis of the data from patients whose cervical length was 15 mm or less found no difference in preterm birth before 34 weeks of gestation (85.7% with cerclage versus 16.7% without; aOR, 1.44; 95% CI, 0.7–8.46).

Due to the small sample sizes of the studies as well as their methodologic limitations, there are insufficient data to recommend for or against cervical cerclage for patients with a multiple gestation and a short cervix on ultrasonography in the second trimester.

Examination-Indicated Cerclage

A 2020 randomized controlled trial compared cerclage versus no cerclage in women with twin pregnancies and asymptomatic cervical dilation of 1–5 cm between 16 0/7 weeks of gestation and 23 6/7 weeks of gestation (187). When comparing the cerclage group with the no-cerclage group, the incidence of preterm birth was significantly decreased as follows: preterm birth before 34 weeks of gestation, 12 of 17 women (70%) versus 13 of 13 women (100%) (RR, 0.71; 95% CI, 0.52–0.96); preterm birth before 32 weeks of gestation, 11 of 17 women (64.7%) versus 13 of 13 women (100%) (RR, 0.65; 95% CI, 0.46–0.92); preterm birth before 28 weeks of gestation, 7 of 17 women (41%) versus 11 of 13 women (84%) (RR, 0.49; 95% CI, 0.26–0.89); and preterm birth before 24 weeks of gestation, 5 of 17 women (30%) versus 11 of 13 women (84%) (RR, 0.35; 95% CI, 0.16–0.75). Based on these limited data, cervical cerclage may be of benefit for women with twin gestation and cervical dilation in the second trimester.

Cervical Pessary

Twin Pregnancy

In twin pregnancy the cervical pessary has been compared with standard pregnancy care (188–190). Two randomized clinical trials that included unselected twin gestations showed no benefit with cervical pessary placement at a mean gestational age of 16–23 weeks of gestation (188, 190). A meta-analysis that included those two trials and a third that recruited only twin pregnancies with a short cervix found similar results (191). Use of the cervical pessary did not reduce the incidence of preterm birth before 34 weeks of gestation (RR, 0.71; 95% CI, 0.29–1.71), perinatal death (RR, 0.89; 95% CI, 0.57–1.38), or respiratory distress syndrome (RR, 1.08; 95% CI, 0.84–1.39). Current evidence does not support the use of cervical pessary to prevent preterm birth or improve perinatal outcomes in twin gestations with a short cervix and in unselected twin gestations (138,180). Cervical pessary is not recommended for prevention of preterm birth in twin pregnancy.

The cervical pessary also has been assessed in twin pregnancy with a short cervix, with conflicting results. Many of the studies have been underpowered and contained methodologic challenges (192–194). A meta-analysis of these randomized trials found that use of the cervical pessary in twin pregnancies with a short cervix did not reduce the risk of spontaneous preterm birth before 34 0/7 weeks of gestation (25% versus 31%; RR, 0.72; 95% CI, 0.25–2.06), perinatal death, or any of the neonatal morbidities (193,194). Cervical pessary is not recommended for prevention of preterm birth in twin pregnancies with a short cervix (Table 1).

▶ *Does activity restriction reduce the risk of preterm birth?*

Restriction of physical activity, including bed rest, limited work, and avoidance of vaginal intercourse, are frequently recommended to reduce the likelihood of preterm birth in pregnancies at risk for indicated and spontaneous birth, despite the absence of benefit and considerable evidence of maternal risk in the literature (195). A randomized controlled trial of 165 pregnant people found no relationship between coitus and risk for recurrent preterm birth (196). A secondary analysis of a randomized trial of intramuscular 17-OHPC for prevention of recurrent preterm birth in women with a cervical length of less than 30 mm in the second trimester noted that preterm birth at less than 37 weeks of gestation was more common among women who reported they were placed on activity restriction (37% versus 17%; $P<.001$) (197). After controlling for potential confounding factors, preterm birth remained more common among those placed on activity restriction (aOR, 2.37; 95% CI, 1.60–3.53). Activity restriction is not recommended to reduce the risk of preterm birth.

Summary of Recommendations

Recommendations based on good and consistent scientific evidence (Level A):

- Because of the relatively high detection rate and predictive value in individuals with prior preterm birth, and because treatment is available, serial endovaginal ultrasound measurement of cervical length beginning at 16 0/7 weeks of gestation and repeated until 24 0/7 weeks of gestation for individuals with a singleton pregnancy and a prior spontaneous preterm birth is recommended.
- For the purpose of prevention of preterm birth, screening and antibiotic treatment for bacterial vaginosis in pregnant individuals without symptoms of vaginitis is not recommended.
- Vaginal progesterone is recommended for asymptomatic individuals without a history of preterm birth with a singleton pregnancy and a short cervix.

- Intramuscular 17-OHPC is not recommended for prevention of preterm birth in patients who do not have a history of spontaneous preterm delivery.
- Patients with a singleton pregnancy and a prior spontaneous preterm birth should be offered progesterone supplementation (either vaginal or intramuscular) in the context of a shared decision-making process incorporating the available evidence and the patient's preferences.
- Cervical pessary is not recommended for prevention of preterm birth in twin pregnancies with a short cervix.

Recommendations based on limited or inconsistent scientific evidence (Level B):

- The cervix should be visualized at the 18 0/7–22 6/7 weeks of gestation anatomy assessment in individuals without a prior preterm birth, with either a transabdominal or endovaginal approach.
- Screening of cervical length with serial endovaginal ultrasonography is not indicated in pregnant individuals without a prior preterm birth.
- Cervical pessary is not recommended for the singleton pregnancy with a short cervix and no history of spontaneous preterm birth.
- Intramuscular 17-OHPC is not recommended for prevention of preterm birth based solely on the indication of multiple gestation.
- Routine prophylactic use of vaginal progesterone to prevent preterm birth in twin pregnancies is not recommended.
- Cervical cerclage is not recommended for prevention of preterm birth based solely on the indication of multiple gestation.

Recommendations based primarily on consensus and expert opinion (Level C):

- Patients with a singleton gestation, a prior spontaneous preterm birth, and a short cervix in the second trimester who are not on progesterone supplementation should be informed of their increased risk of preterm birth, the two treatment options available (vaginal progesterone and cerclage), and the uncertainty about which management course is best in the context of a shared decision-making process.
- Patients with a singleton gestation, prior spontaneous preterm birth, and a short second-trimester cervix who are on progesterone supplementation should be informed of their increased risk of preterm birth, and cerclage may be offered in addition to continuation of progesterone.
- Activity restriction is not recommended to reduce the risk of preterm birth.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and July 2020. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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