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Prediction and Prevention of Preterm Birth

Preterm birth is the leading cause of neonatal mortality in the United States, and preterm labor precedes approximately 50% of preterm births (1, 2). Neonatal intensive care has improved the survival rate for neonates at the cusp of viability, but it also has increased the proportion of survivors with disabilities (3). The incidence of multiple births also has increased along with the associated risk of preterm delivery (4). The purpose of this document is to describe the various methods proposed for identifying and treating asymptomatic women at increased risk of preterm birth and the evidence for their roles in clinical practice.

Background

Spontaneous preterm birth includes birth that follows preterm labor, preterm spontaneous rupture of membranes, and cervical insufficiency, but does not include indicated preterm delivery for maternal or fetal conditions (5). The preterm birth rate (birth at less than 37 completed weeks of gestation per 100 total births) increased more than 20% from 1990 to 2006. However, decreases in birth rates for both early preterm birth (earlier than 34 weeks of gestation) and late preterm birth (34 0/7–36 6/7 weeks of gestation) contributed to a decrease in the overall preterm birth rate between 2008 (12.3%) and 2009 (12.18%) (1). The risk of poor birth outcome generally decreases with advancing gestational age. Although risks are greatest for neonates born before 34 weeks of gestation, infants born after 34 weeks of gestation but before 37 weeks of gestation are still more likely to experience delivery complications, long-term impairment, and early death than those born later in pregnancy (6).

Infants born prematurely have increased risks of mortality and morbidity throughout childhood, especially during the first year of life. In the absence of more comprehensive tests of fetal and neonatal status, gestational age is a common surrogate for presumed functional maturity. Although age is related to maturity, no easily identified gestational age boundary exists between a premature neonate and a mature neonate. The risks of perinatal, neonatal, and infant morbidity and mortality are lowest for infants born between 39 0/7 weeks of gestation and 40 6/7 weeks of gestation. These risks increase as gestational age at birth decreases, with morbidity reported at 37 weeks of gestation and even 38 weeks of gestation in some series (7, 8).

Risk Factors

One of the strongest clinical risk factors for preterm birth is a prior preterm birth (9). Maternal history of preterm birth is commonly reported to confer a 1.5-fold to 2-fold increased risk in a subsequent pregnancy. Importantly, the number of prior preterm births and the gestational age at the prior delivery significantly affect the recurrence risk of preterm birth (10). A preterm birth followed by delivery at term confers lower risk than the opposite

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sequence (10, 11). For women with a prior preterm twin birth, the risk of preterm birth in a subsequent singleton gestation varies according to the gestational age at twin delivery, with a recurrence risk as high as 40% when a prior twin birth was before 30 weeks of gestation (12, 13).

Short cervical length measured by transvaginal ultrasonography also has been associated with an increased risk of preterm birth (14–16). Short cervical length is most commonly defined as less than 25 mm, usually before 24 weeks of gestation, but up to 28 weeks of gestation in some series. It is a cutoff that has been associated with an increased risk of preterm birth in screened populations (15, 17). Clinically, the shorter the cervical length, the greater the risk of preterm birth.

Additional proposed risk factors for preterm birth include aspects of obstetric and gynecologic history, demographic characteristics, current pregnancy complications, and behavioral factors. However, data are inconsistent about whether these factors are actually causative for preterm birth. Preconception care allows an opportunity to assess risk factors and provide counseling for women with risk factors that can be modified, such as smoking and optimal control of underlying chronic diseases (18).

A history of cervical surgery, including conization and loop electrosurgical excision procedure, traditionally has been thought to be a risk factor for preterm birth because of associated cervical injury, but this relationship also may be related to environmental, factors, behavioral factors, or both (such as smoking) that underlie the progression of cervical dysplasia (19, 20). Uterine instrumentation (eg, dilation and curettage) also has been associated with an increased risk of preterm birth in some, but not all, studies; the mechanism is unclear, but intrauterine microbial colonization, injury to the endometrium, or both, together with host and environmental factors, has been suggested (21).

Other 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. However, treatments for any of these potential risk factors have not been definitively demonstrated to result in a decreased risk of preterm birth. Early studies of the role of UTIs in preterm birth have demonstrated an association between untreated asymptomatic bacteriuria in early pregnancy and increased rates of preterm birth (22, 23). However, subsequent meta-analyses have reported conflicting results. One early report showed that untreated asymptomatic bacteriuria significantly increased rates of low birth weight and preterm delivery (24). However, later analyses, including one study of more than 25,000 births, and a Cochrane review, have failed to confirm this finding (25, 26). Therefore, the association reported between treating UTIs in pregnancy and preventing preterm birth may be related to preventing progression of subclinical infections to pyelonephritis (25, 27). In addition, women with periodontal disease have an increased risk of preterm birth that is not affected by periodontal care. This suggests that the increased risk is caused by associated traits rather than a causal linkage (28–31). In fact, active treatment of periodontitis in pregnancy has been shown in one study to potentially increase the risk of spontaneous preterm birth (30).

Behavioral risk factors for preterm birth include low maternal prepregnancy weight, smoking, substance abuse, and short interpregnancy interval. Low maternal body mass index (less than 19.8; calculated as weight in kilograms divided by height in meters squared) has been regularly found to be associated with an increased risk of preterm birth (32, 33). Smoking is associated with an increased risk of preterm birth and, unlike most other risks, is amenable to intervention during pregnancy (34, 35). An epidemiologic review of three U.S. studies showed that the risk of adverse birth outcomes, including preterm birth, was lowest when the interpregnancy interval was 18–23 months and increased when the interval fell outside of this range (36).

Screening Modalities

Transvaginal cervical ultrasonography has been shown to be a reliable and reproducible way to assess the length of the cervix (37). This is in contrast to transabdominal ultrasound evaluation of the cervix. Unlike the transabdominal approach, transvaginal cervical ultrasonography is not affected by maternal obesity, position of the cervix, and shadowing from the fetal presenting part (38, 39). In addition, unlike digital examination, transvaginal ultrasonography can help identify the presence of other ultrasound risk markers for preterm delivery, such as the presence of intraamniotic debris (a possible sign of intrauterine microbial colonization) and choriodecidual separation (40, 41).

When performed by trained operators, cervical length screening by transvaginal ultrasonography is safe, highly reproducible, and more predictive than transabdominal ultrasound screening. Using a method in which the transvaginal probe is placed in the anterior fornix of the vagina with an empty maternal bladder results in measurements with interobserver variation of 5–10% (37). Measurement of the cervical length in this manner identifies a faint line of echodensity between internal and external os, avoiding undue pressure on the cervix that might increase its apparent length. The cervical length is the shortest of three measurements taken between calipers placed at the internal os and external os (15, 42). As an independent finding, cervical funneling does not add

appreciably to the preterm delivery risk associated with a shortened cervical length (43).

Other specific tests and monitoring modalities, such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring have been proposed to assess a woman's risk of preterm delivery. However, available interventional studies based on the use of these tests for screening asymptomatic women have not demonstrated improved perinatal outcomes (44–46). Thus, these methods are not recommended as screening strategies.

In addition, interventions, such as pharmacotherapy with indomethacin or antibiotics, activity restriction, or supplementation with omega-3 fatty acids have not been evaluated in the context of randomized trials for women with short cervical length, and are not recommended as clinical interventions for women with an incidentally diagnosed short cervical length. Although maternal dietary fish consumption has been associated with a reduced risk of preterm birth, supplementation with omega-3 fatty acids was not found to reduce the risk of preterm birth in a large randomized trial of women with a prior preterm spontaneous birth who received 17α-hydroxyprogesterone caproate (47, 48). Randomized placebo-controlled trials of women taking vitamin C and vitamin E, supplemental calcium, and protein also have not been associated with a decreased risk of preterm birth (49–53).

Clinical Considerations and Recommendations

▶ *How should women with a previous spontaneous preterm birth be evaluated for risk of subsequent preterm birth?*

The evaluation of women with a prior spontaneous preterm birth should include obtaining a detailed medical history, reviewing comprehensively aspects of all previous pregnancies, reviewing risk factors, and determining their candidacy for prophylactic interventions, such as progesterone supplementation, cervical cerclage, or both.

A comprehensive review of all previous pregnancies is an important step in the evaluation of women at risk of preterm birth because the most important historical risk factor for recurrent preterm birth is a prior spontaneous preterm birth, including births in the mid-to-late second trimester (54). It can be difficult to differentiate spontaneous preterm birth from indicated preterm birth, but an effort to establish this distinction should be an integral part of history taking. The review of medical records and placental pathology results can be helpful in this process. Spontaneous preterm births are those in which the onset of parturition was spontaneous, regardless of whether the process was later augmented. Rather than determining whether a prior preterm birth was spontaneous, it may be easier first to exclude a prior preterm birth that was obviously indicated (ie, initiated by the obstetric care provider for a medical condition that threatened maternal health, fetal health, or both).

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

A woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16–24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth (55–57) (Table 1). Whether such a woman might additionally benefit from cervical cerclage placement also has been studied.

A multicenter, randomized trial examined the role of serial transvaginal cervical length screening, with cerclage placement for short cervical length, among women with singleton gestations and prior spontaneous preterm births at less than 34 weeks of gestation, including some women who received 17α-hydroxyprogesterone caproate (58). Women in this trial underwent serial cervical length screening once every 2 weeks, starting at 16 weeks of gestation until 23 weeks of gestation. If the length of the cervix was noted to be between 25 mm and 29 mm, the screening frequency was increased to once a week. If the cervical length was less than 25 mm, women were randomized to undergo cerclage or not to undergo cerclage. The primary study outcome was preterm birth at less than 35 weeks of gestation, for which no significant difference was detected (relative risk [RR], 0.78; 95% confidence interval [CI], 0.58–1.04) (58). However, placement of a cerclage was associated with significant reductions in deliveries before 24 weeks of gestation (RR, 0.44; 95% CI, 0.21–0.92) and before 37 weeks of gestation (RR, 0.75; 95% CI, 0.60–0.93) as well as in perinatal death (RR, 0.54; 95% CI, 0.29–0.99) when compared with the group that did not undergo cerclage (58). In a planned secondary analysis, cerclage for cervical length less than 15 mm was associated with a significant decrease in preterm birth at less than 35 weeks of gestation (RR, 0.23; 95% CI, 0.08–0.66) (58). Based on the pooled results of five clinical trials, in a singleton pregnancy with prior spontaneous preterm birth at less than 34 weeks of gestation and cervical length less than 25 mm before 24 weeks of gestation, cerclage was associated with a 30% reduction in the risk of preterm birth at less than 35 weeks of gestation (28% versus 41%; RR, 0.7; 95% CI, 0.55–0.89) and a 36% reduction in compos-

Table 1. Selected Studies on Progesterone Supplementation for the Prevention of Preterm Delivery in Singleton Gestations

Study	Dosage	Population
Meis, 2003*	17α-hydroxyprogesterone caproate (250 mg weekly injections)	Women with a documented history of a spontaneous singleton preterm birth at less than 37 weeks of gestation; cervical length not measured at entry; treatment initiated between 16 weeks of gestation and 20 weeks of gestation and continued until 36 weeks of gestation or delivery, whichever occurred first
da Fonseca, 2003†	Vaginal progesterone (100 mg daily)	High-risk women with a history of spontaneous singleton preterm birth; treatment initiated at 24 weeks of gestation and continued until 34 weeks of gestation
O'Brien, 2007‡	Vaginal progesterone (90 mg daily)	Women with a history of spontaneous preterm birth randomized and treated; cervical length measured at entry (mean length, 37 mm); treatment initiated between 18 weeks of gestation and 22 6/7 weeks of gestation and continued until 37 weeks of gestation, occurrence of premature rupture of membranes, or preterm delivery
Fonseca, 2007§	Micronized progesterone gel capsules (200 mg vaginally daily)	Asymptomatic women with a very short cervical length (15mm or less); 90% of the women had a singleton gestation and 85% had no prior preterm delivery; treatment initiated at 24 weeks of gestation and continued until 34 weeks of gestation
Hassan, 2011‖	Vaginal progesterone gel (90 mg daily)	Women with a singleton gestation with a previous preterm birth between 20 weeks of gestation and 35 weeks of gestation; patients were randomized between 20 weeks of gestation and 23 6/7 weeks of gestation; treatment continued until 36 6/7 weeks of gestation, rupture of membranes, or delivery, whichever occurred first.
Hassan, 2011‖	Vaginal progesterone gel (90 mg daily)	Only women without prior preterm birth; patients were randomized between 20 weeks of gestation and 23 6/7 weeks of gestation; treatment continued until 36 6/7 weeks of gestation, rupture of membranes, or delivery, whichever occurred first.

*Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network [published erratum appears in N Engl J Med 2003;349:1299]. N Engl J Med 2003;348:2379–85.

†da Fonseca EB, Bittar RE, Carvalho MH, Zagaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419–24.

‡O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Gynecol 2007;30:687–96.

§Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. Fetal Medicine Foundation Second Trimester Screening Group. N Engl J Med 2007;357:462–9.

‖Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, 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. PREGNANT Trial. Ultrasound Obstet Gynecol 2011;38:18–31.

ite perinatal mortality and morbidity (16% versus 25%; RR, 0.64; 95% CI, 0.45–0.91) (58–60).

Although the single largest trial of cerclage for preterm birth prevention in high-risk women did not find benefit for the primary study outcome, available evidence suggests that, in women with a current singleton pregnancy, prior spontaneous preterm birth at less than 34 weeks of gestation and short cervical length (less than 25 mm) before 24 weeks of gestation, cerclage placement is associated with significant decreases in preterm birth outcomes, offers perinatal benefits, and may be considered in women with this combination of history and ultrasound findings (58, 60). Insufficient evidence exists to assess whether progesterone and cerclage together have an additive effect in reducing the risk of preterm birth in women at high risk for preterm birth (61).

No evidence exists to support the addition of an alternative form of progesterone to the current progesterone treatment (eg, adding a vaginal form to an intramuscular form), if a short cervix is identified in a woman with a prior preterm birth who is already receiving preventive progesterone therapy. Also, there is no evidence to suggest that switching from treatment with intramuscular progesterone to treatment with vaginal progesterone is beneficial if a short cervix is identified.

▶ *Should a woman with a current singleton pregnancy without a history of preterm birth be screened for a risk of preterm birth?*

In general, women in this clinical scenario are at a low risk of preterm birth. However, if second trimester transabdominal scanning of the lower uterine segment suggests that the cervix may be short or have some other abnormality, it is recommended that a subsequent transvaginal ultrasound examination be performed to better visualize the cervix and establish its length (15). Until recently, routine cervical length evaluation in women at a low risk of preterm delivery was not advocated because, like other factors associated with a potentially higher preterm birth risk, no effective treatments were available to reduce that risk. Recent randomized trials that investigated the use of vaginal progesterone in women with a short cervix diagnosed through screening have initiated consideration of whether the current standard for evaluating the cervix should be changed.

A European trial that enrolled women with a very short cervical length (15 mm or less) demonstrated a lower risk of preterm birth in those treated with vaginal progesterone suppository, 200 mg daily, compared with those who were treated with a placebo (62). In this study, only 1.7% of the 24,640 women screened at 20–25 weeks of gestation (median, 22 weeks of gestation) were found to have a cervical length less than or equal to 15 mm and, therefore, to be eligible for the trial.

In a subsequent randomized trial, the use of vaginal progesterone gel, 90 mg daily, was associated with a decrease in spontaneous preterm birth at less than 33 weeks of gestation (9% versus 16%; RR, 0.55; 95% CI, 0.33–0.92) and a decrease in composite neonatal morbidity and mortality (8% versus 14%; RR, 0.57; 95% CI, 0.33–0.99) among asymptomatic women with a cervical length of 10–20 mm at 19–23 6/7 weeks of gestation (16). All the women in this study had singleton gestations, with a 16% incidence of prior preterm birth. Analysis of only women without prior preterm birth confirmed significant benefit of progesterone in preventing preterm birth before 33 weeks of gestation in this study (16). Even taking into account the large number of women needed to be screened to identify those at risk, recent decision and economic analyses concluded that universal ultrasound screening for short cervical length and treatment with vaginal progesterone was cost-effective (63, 64).

Proponents of universal cervical length screening of women without a prior preterm birth cite the following points in support of this practice: it has the potential to reduce the preterm birth rate; high quality evidence exists to support efficacy of treatment for positive test results (ie, cervical length of 20 mm or less); and it is cost effective, safe, accepted by patients, and widely available. Opponents of this approach raise the following concerns: quality assurance of the screening test; lack of availability of screening and of patient access to qualified imaging centers in some areas; and the potential for patients to receive unnecessary or unproven interventions.

The American College of Obstetricians and Gynecologists recognizes that both sides of this debate raise valid issues. Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered. Practitioners who decide to implement universal cervical length screening should follow one of the protocols for transvaginal measurement of cervical length from the clinical trials on this subject. Protocol citations are listed in Table 1.

▶ *What interventions have been shown to be beneficial for reducing the risk of preterm birth in women who do not have a history of preterm birth but who are found to have a short cervical length?*

Cerclage and progesterone are the two interventions that have been evaluated in randomized trials for effectiveness in preventing preterm birth in women with singleton gestations without a prior preterm birth (Fig. 1).

Vaginal progesterone has been studied as a management option to reduce the risk of preterm birth in asymptomatic women with singleton gestations without prior preterm birth with a very short cervical length, defined as less than or equal to 20 mm at up to 24 weeks of gestation. In a randomized placebo-controlled trial, treatment with vaginal micronized progesterone, 200 mg daily, was associated with a 44% decrease in spontaneous preterm birth at less than 34 weeks of gestation among asymptomatic women with a cervical length of 15 mm or less at 20–25 weeks of gestation (19% versus 34%; RR, 0.56; 95% CI, 0.36–0.86) (62). In this study, 90% of the women had a singleton gestation, and 85% had no prior preterm birth (62).

In another recent randomized placebo-controlled trial, treatment with vaginal progesterone gel, 90 mg daily, was associated with a 45% decrease in spontaneous preterm birth at less than 33 weeks of gestation (9% versus 16%; RR, 0.55; 95% CI, 0.33–0.92) and a 43% decrease in composite neonatal morbidity and mortality (8% versus 14%; RR, 0.57; 95% CI, 0.33–0.99) among asymptomatic women with a cervical length of 10–20.9 mm at 19–23 6/7 weeks of gestation (16). All the women in this study had singleton gestations, with a 16% incidence of prior preterm birth. Analysis of only women without prior preterm birth confirmed significant benefit

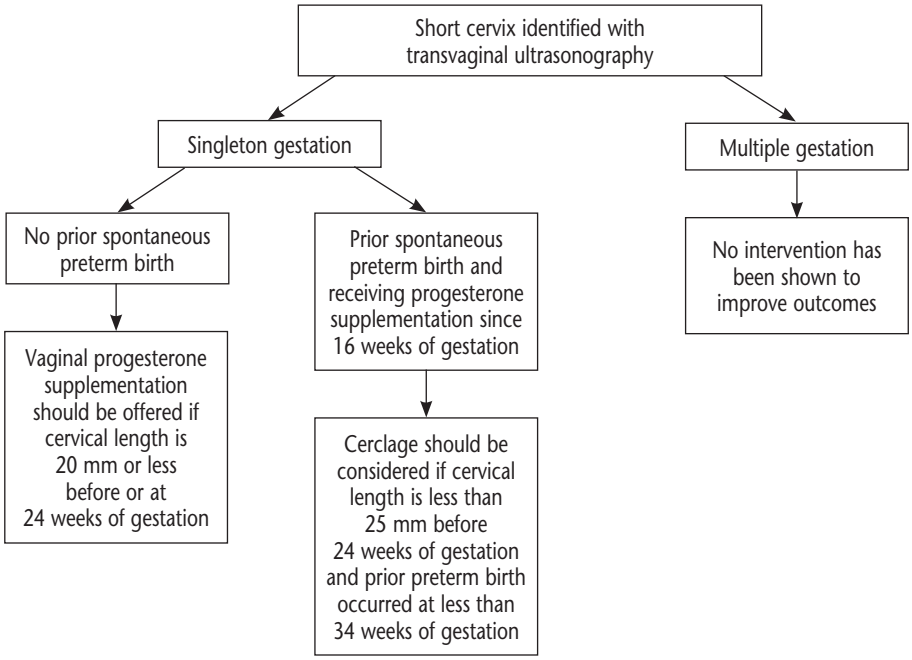

Fig. 1. Algorithm for the management of short cervical length in the second trimester.

of treatment with progesterone in preventing preterm birth before 33 weeks of gestation in this study (16). Therefore, vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20 mm before or at 24 weeks of gestation.

In contrast, for women in this otherwise low-risk population, cerclage placement in women with a cervical length less than 25 mm detected between 16 weeks of gestation and 24 weeks of gestation has not been associated with a significant reduction in preterm birth at less than 35 weeks of gestation [RR, 0.76; 95% CI, 0.52–1.15] (59). Even cerclage placement for detection of a cervical length of 15 mm or less in women at 22–24 weeks of gestation has not been shown to significantly decrease the rate of preterm birth (at less than 33 weeks of gestation) (RR, 0.84; 95% CI, 0.54–1.31) (65).

In one trial of women with an incidentally diagnosed short cervix (less than or equal to 25 mm at 18–22 weeks of gestation), open-label randomization to placement of a cervical pessary or expectant management (no pessary) was studied (66). In this trial of 385 women, the rate of spontaneous delivery at less than 34 weeks of gestation was significantly lower in the pessary group than in the no pessary group (6% compared with 27%; OR, 0.18; 95% CI, 0.08–0.37). If the results of this small trial are validated, cervical pessary placement may have additional benefit for prevention of preterm birth in otherwise low-risk women with a short cervix.

▶ *Does cerclage placement or progesterone treatment decrease the risk of preterm birth in women with multiple gestations?*

Available data regarding the efficacy of cerclage placement, progesterone supplementation, or both for the reduction of preterm birth risk in women with multiple gestations with a short cervical length with or without a prior preterm birth do not support their use (67). Cerclage may increase the risk of preterm birth in women with a twin pregnancy and ultrasonographically detected cervical length less than 25 mm and is not recommended. In a meta-analysis of randomized trials, cerclage performed in women with a twin pregnancy and a cervical length less than 25 mm was actually associated with a significant twofold increase in the rate of preterm birth (RR, 2.2; 95% CI, 1.2-4) (59). Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations (68–72). Currently, no data are available regarding the efficacy of any other interventions to reduce the risk of preterm birth in women with multiple gestations and a short cervix, and the use of any such alternative measures cannot be recommended outside of formal clinical trials.

Summary of Recommendations and Conclusions

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

- A woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16–24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth.
- Vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20 mm before or at 24 weeks of gestation.
- Tests, such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring, are not recommended as screening strategies.
- Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations.

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

- Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered.
- Insufficient evidence exists to assess if progesterone and cerclage together have an additive effect in reducing the risk of preterm birth in women at high risk for preterm birth.
- Cerclage may increase the risk of preterm birth in women with a twin pregnancy and an ultrasonographically detected cervical length less than 25 mm and is not recommended.

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

- Practitioners who decide to implement universal cervical length screening should follow one of the protocols for transvaginal measurement of cervical length from he clinical trials on this subject. Protocol citations are listed in Table 1.

Proposed Performance Measure

Percentage of women with a prior spontaneous preterm birth who are offered progesterone supplementation

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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 1990 and March 2012. 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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