

CLINICAL PRACTICE

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Prevention of Preterm Parturition

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A woman presents for prenatal care in the first trimester of her third pregnancy. Her first child was born at 30 weeks of gestation after preterm labor. Her second pregnancy ended in delivery at 19 weeks of gestation. How would you recommend reducing the risk of preterm birth in this pregnancy?

THE CLINICAL PROBLEM

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In the United States, the annual rate of preterm births (before 37 weeks of gestation) reached a peak of 12.8% in 2006 and was 11.7% in 2011.¹ The rate in the United States remains nearly twice the rate in European nations.²

Premature birth in the United States accounts for 35% of deaths in the first year of life^{3,4} and estimated annual costs exceeding \$26 billion.⁵ Rates of death in the first year of life and long-term morbidity such as neurobehavioral impairment are inversely related to gestational age at birth. Neonates born before 24 weeks of gestation rarely survive without serious handicaps. Among neonates born at or after 24 weeks of gestation, mortality and morbidity decline with advancing weeks of gestation. Serious neurodevelopmental complications are uncommon after 32 weeks of gestation; however, neonates born before 36 weeks of gestation often have difficulties with respiration, thermoregulation, and feeding, as well as increased risks of health problems and death in childhood.⁶

Approximately 25% of preterm births in developed nations are iatrogenic, reflecting cases in which maternal or fetal conditions make early delivery a safer choice than continued pregnancy, for the mother, the fetus, or both. Multifetal pregnancies account for about one fifth of all preterm births; 50% of twin births and more than 90% of triplet births are preterm. Most singleton preterm births occur after the spontaneous early onset of the parturitional process. This article focuses on strategies to prevent preterm birth.



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RISK FACTORS

Factors associated with a risk of preterm birth may be identified before pregnancy, at conception, or during pregnancy. Major risk factors for spontaneous preterm birth in cases of singleton pregnancies include black maternal race, previous pregnancy with an adverse outcome, genitourinary infection, smoking, extremes of body weight, and social disadvantage. Maternal depression, prepregnancy stress, poor diet, assisted fertility, and periodontal disease are also associated with preterm birth.⁵

Black women have a higher risk of preterm birth than do women of any other racial or ethnic background. In 2011, rates of birth before 37 weeks of gestation were 1.6 times as high among non-Hispanic black women as among non-Hispanic white women (16.8% vs. 10.5%), and rates of birth before 32 weeks of gestation were 2.5 times as high among non-Hispanic black women as among non-Hispanic

KEY CLINICAL POINTS

PREVENTION OF PRETERM PARTURITION

- Despite advances in neonatal care, preterm birth remains a leading cause of infant death in the United States, especially among blacks.
- Systemic changes in reproductive health care to reduce the incidence of multifetal pregnancies and scheduled births before 39 weeks of gestation that lack a medical indication have been temporally associated with decreased preterm birth rates.
- Strategies to identify and treat medical risk factors in early pregnancy (e.g., genitourinary infection and poor nutrition) have not been effective in reducing preterm birth rates.
- Previous preterm birth and a short cervix (≤ 20 mm, as measured by transvaginal ultrasonography) are major risk factors for preterm birth.
- The use of progesterone supplementation in women with a previous preterm birth, a short cervix, or both was shown in randomized trials to reduce the frequency of preterm birth and is recommended for women with these risk factors.
- Cervical cerclage reduces the risk of recurrent preterm birth among women with a short cervix.

white women (3.8% vs. 1.5%).¹ The racial disparity persists after adjustment for social, educational, economic, and medical risk factors.^{5,7}

A previous preterm birth is a strong and easily identified risk factor for future preterm births; a preterm birth increases the risk of future preterm births by a factor of 1.5 to 2. The number, sequence, and weeks of gestation of previous births all affect the risk of recurrence, which ranges from less than 15% among women with one preterm birth after 32 weeks of gestation that was followed by a birth at term, to nearly 60% among women with a history of two or more births before 32 weeks of gestation.⁸ Spontaneous preterm births are also more common among women with a history of giving birth between 16 weeks and 20 weeks of gestation⁹ or with a history of stillbirth before 24 weeks of gestation.¹⁰ However, most women who give birth before term do not have multifetal pregnancies or major risk factors. Risk assessment in the general obstetrical population is limited by the high prevalence and low relative risk of preterm delivery associated with risk factors such as genitourinary infection, social disadvantage, depression, stress, and poor nutrition. In as many as half of preterm births, the mother has no evident risk factors.⁵

Short cervical length (i.e., values below the 10th percentile for gestational age), as measured with the use of transvaginal ultrasonography at 18 to 24 weeks of gestation (Fig. 1) is a consistent predictor of an increased risk of preterm delivery,^{11,12} regardless of other factors.¹³ The risk increases as cervical length decreases in the second trimester; the risk associated with a cer-

vical length below the 10th percentile (25 mm) is 25 to 30%, and the risk associated with a cervical length at or below the 3rd percentile (15 mm) is 50%.¹¹ Among women who have had a preterm birth, the risk of recurrence in a subsequent pregnancy ranges from less than 10% when the cervical length at 22 or 24 weeks is above 35 mm to more than 35% when the cervical length is below 25 mm.¹⁴ A short cervix is relatively uncommon among women who have no risk factors for preterm birth; however, a short cervix confers an increase in the relative risk of preterm birth that is similar among nulliparous women and those with a previous birth at term.¹⁵

NATURAL HISTORY

Cervical preparation for birth begins soon after conception.¹⁶ The two phases of cervical change that have been described are softening and ripening.^{16,17} Softening occurs slowly and is characterized by an increase in cervical compliance (with maintenance of tissue competence) in an environment that is high in progesterone and low in estrogen.¹⁷ Ripening, defined by loss of tissue compliance and decreased tensile strength, occurs during the weeks or days preceding active labor.¹⁶ In normal parturition, these cervical changes are followed by decidual activation and myometrial contractions.¹⁸ Decidual activation is paracrine signaling from the fetus through the amniotic fluid and across the membranes to the underlying maternal decidua and myometrium, ultimately causing contractions. This process normally occurs in late pregnancy as the fetal pituitary-adrenal axis achieves maturity. The steps in decidual activation can be activated prematurely in



Figure 1. Ultrasonogram of the Cervix.

A midline sagittal ultrasonographic image of the uterine cervix at 22 weeks of gestation shows that the length of the closed portion of the cervical canal (dotted line with plus signs) is 2.12 cm (21 mm).

any sequence by choriodecidual inflammation, decidual hemorrhage, membrane rupture, uterine trauma or stretching, or fetal signals of compromise.¹⁸ Genetic and environmental factors affect these pathways.¹⁹ Active labor begins when contractions persist and cause further cervical dilatation and thinning over a period of hours before birth.

The contractions associated with preterm labor are painful when they are sustained and precede clinically significant cervical preparation (e.g., contractions occurring after decidual hemorrhage). More commonly, myometrial contractions occur after cervical softening and decidual activation, a sequence characterized clinically by mild but persistent pelvic pressure, cramps, increased vaginal discharge (mucus), and occasional spotting during several days or weeks until labor begins, the fetal membranes rupture, or both. This presentation is typical in women with a short cervix.

STRATEGIES AND EVIDENCE

Strategies to prevent preterm birth have traditionally emphasized early prenatal care as providing an opportunity to identify and treat prematurity-related risk factors, but this approach has not reduced the incidence of preterm birth. Improved access to prenatal care is associated with lower rates of preterm birth, but the linkage is apparently related more to the high rates among women who receive no prenatal care than to the content of care received.⁵ Adequately powered randomized trials of interventions aimed at nutri-

tional deficiencies (vitamins C and E,²⁰ calcium,²¹ and n-3 fatty acids²²), genital tract microorganisms (bacterial vaginosis²³ and *Trichomonas vaginalis*²⁴), or treatment of periodontal disease²⁵ have not shown reductions in preterm births among women with risk factors or those without risk factors.

Nevertheless, the rate of preterm births in the United States has fallen annually since 2006⁴; the percentage of births before 34 weeks of gestation declined from 3.7% in 2006 to 3.4% in 2011.²⁶ The decrease coincided with the adoption of fertility practices that reduce the likelihood of multifetal pregnancies (transfer of fewer embryos)²⁷ and with structured quality-improvement efforts by regional^{28,29} and national^{30,31} organizations to promote adherence to professional guidelines³² to schedule late preterm delivery (at 34 to 36 weeks of gestation) and near-term delivery (at 37 to 38 weeks of gestation) only for valid medical indications. Increased use of supplemental progesterational agents (progestogens) and cervical cerclage in women with a previous preterm birth, a short cervix, or both may have contributed to the decline.

PROGESTERONE THERAPY

Treatment with progesterone was initially studied because of evidence that labor begins when the ratio of progesterone activity to estrogen activity is reversed or when progesterone activity is blocked, resulting in cervical ripening and uterine contractility.^{33,34} Progesterone causes inhibition of cervical ripening, reduction of myometrial contractility through suppression of oxytocin-receptor synthesis and function, and modulation of inflammation.³⁵ A meta-analysis of six studies suggested that prophylactic weekly intramuscular injections of 17 alpha-hydroxyprogesterone caproate (17OHP) reduced the incidence of recurrent preterm birth.³⁶ Some, but not all, larger randomized trials confirmed these results. For example, progesterone (100-mg vaginal suppositories administered daily) significantly reduced the incidence of preterm delivery, as compared with placebo (13.8% vs. 28.5%), in a trial involving high-risk women (94% had had a previous preterm birth).³⁷ A placebo-controlled trial of weekly 250-mg injections of 17OHP in women with a singleton gestation and a history of spontaneous preterm birth showed a 34% reduction in the risk of birth before 37 weeks of gestation among women who received active treatment as

compared with those who received placebo³⁸ (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

In contrast, a third trial, in which women with a previous preterm birth were randomly assigned to receive progesterone vaginal gel (90 mg daily) or placebo, showed no significant effect on the risk of birth before 32 weeks of gestation.³⁹ However, very few of the participants had a short cervix. In another study, which required a cervical length of 10 to 20 mm but not previous preterm delivery for enrollment, the same progesterone preparation (vaginal gel, 90 mg daily) resulted in a 45% decrease in the risk of birth before 33 weeks of gestation, as compared with placebo (8.9% vs. 16.1%), with a corresponding reduction in perinatal morbidity.⁴⁰ A similar reduction in the risk of preterm delivery was observed with progesterone (200-mg vaginal capsules) in a trial involving women with a cervical length of 15 mm or less before 25 weeks of gestation⁴¹; however, only 1.7% of the women who were screened had a cervical length in this range. A trial using a broader definition of a short cervix (<30 mm at 16 to 23 weeks of gestation) showed no benefit of 17OHPC.⁴² Progesterone treatment has not been shown to reduce the rate of preterm birth among women with a cervical length of more than 20 mm³⁹ (Fig. 2) or with multifetal gestations.^{43,44}

CERVICAL CERCLAGE

Cerclage, an encircling suture placed around the cervix before or during pregnancy to correct structural weakness or defects, has been a controversial treatment for a short cervix. In a randomized trial comparing cerclage with observation in women with a previous early preterm birth and a short cervix (<25 mm), the frequency of birth before 35 weeks was not significantly reduced with cerclage (32%, vs. 42% with observation; $P=0.09$)⁴⁵; a preplanned analysis indicated a significant benefit in the subgroup of women with a cervical length of less than 15 mm. A meta-analysis of five trials of cerclage for a short cervix (<25 mm) involving women with a previous preterm birth showed that cerclage reduced the frequency of birth before 35 weeks of gestation (relative risk, 0.70; 95% confidence interval, 0.55 to 0.89) and similarly reduced the risk of perinatal mortality and morbidity.⁴⁶ However, the trials of cerclage for women with a short cervix were designed and performed before progesterone

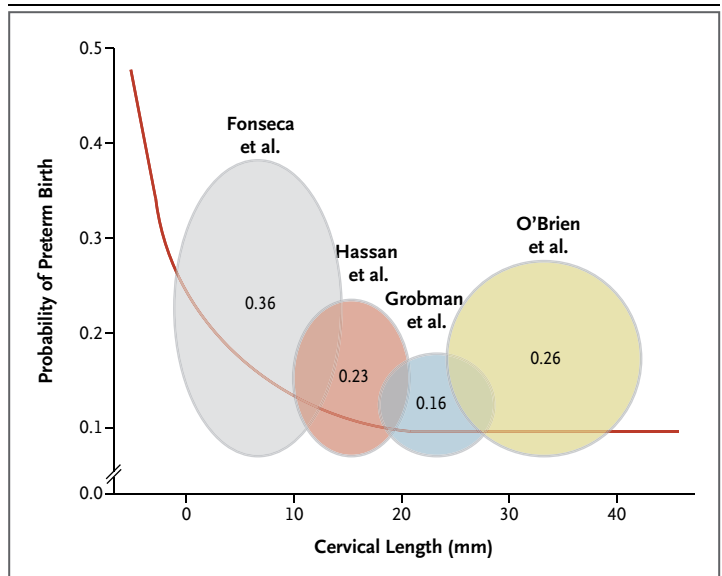


Figure 2. Cervical Length in Women Enrolled in Studies of the Use of Progestogens as Prophylaxis against Preterm Birth.

The risk of preterm birth according to cervical length in women enrolled in four randomized, controlled trials of prophylactic progestogens³⁹⁻⁴² is shown. The red line indicates the risk of preterm birth according to measurements of cervical length in an untreated population.¹¹ The four ovals indicate the probability of preterm birth according to the range of cervical length among women treated with progestogens in the four studies. The height of the oval and the number in the oval reflect the rate of birth before 35 weeks of gestation in the placebo group in each study. The ovals do not indicate the sample size in the trials.

were used for that indication. Available studies suggest that vaginal progesterone and cervical cerclage are similarly effective in reducing the risk of preterm birth among high-risk women,⁴⁷ but randomized, controlled trials have not directly compared these interventions.

These data underlie current recommendations^{48,49} to prescribe vaginal progesterone for women with a short cervix who have not had a previous preterm birth and to prescribe 17OHPC for women who have had a previous preterm birth. For women with a previous preterm birth, cerclage is also advised if the cervical length is less than 25 mm before 24 weeks of gestation.⁴⁶ The role of supplemental cerclage in women with a short cervix but no previous preterm birth is uncertain.

The relationship between a short cervix and an increased risk of preterm birth was initially interpreted as evidence of diminished cervical competence,¹¹ but the recognition that progesterone treatment reduces the risk of preterm birth among women with a short cervix^{40,41} has

altered this view. A short cervix in a singleton pregnancy is considered to indicate the early onset of parturition rather than cervical weakness.⁵⁰

CLINICAL CARE

Ultrasonographic Screening for a Short Cervix

At or soon after the initial prenatal visit, a thorough review of a woman's previous pregnancies and risk factors for prematurity and an ultrasonographic examination to document the location of the gestational sac, the number of fetuses, and the number of weeks of gestation are customarily performed. Women with a previous spontaneous birth at 16 to 36 weeks of gestation, including stillbirth before 24 weeks, are candidates for prophylaxis beginning at 16 weeks of gestation. Such women should undergo cervical ultrasonography between 16 weeks and 24 weeks of gestation to determine whether they are candidates for cerclage (Fig. 3).

The optimal strategy for identifying women with a short cervix is uncertain. One proposed strategy is universal transvaginal ultrasonographic screening of the cervix at 18 to 24 weeks of gestation.⁵¹ However, this approach requires large numbers of skilled ultrasonographers and carries a substantial risk that women with borderline cervical-length measurements (slightly more than 20 mm) will be subjected to repeat examinations, unneeded therapy, or both ("indication creep").⁵² Another possible strategy is to selectively exclude women from screening if a transabdominal ultrasonographic examination indicates a low likelihood of a short cervix; however, the reproducibility of transabdominal imaging of the cervix is uncertain. A third option — performing selective transvaginal screening on the basis of risk factors for preterm birth — is limited by the high prevalence and low positive predictive values of many risk factors.

Data from clinical trials comparing screening strategies are lacking. However, cost-effectiveness analyses have suggested that performing universal transvaginal screening (with progesterone prescribed for women with a cervical length ≤ 15 mm) is more cost-effective than prescribing progesterone for all women who have had a previous preterm birth, regardless of whether the cervical length has been measured.^{53,54} These analyses were predicated on the assumption that the risk of preterm birth would be reduced by 45 to 50% among women with a short cervix who had been treated with progesterone.

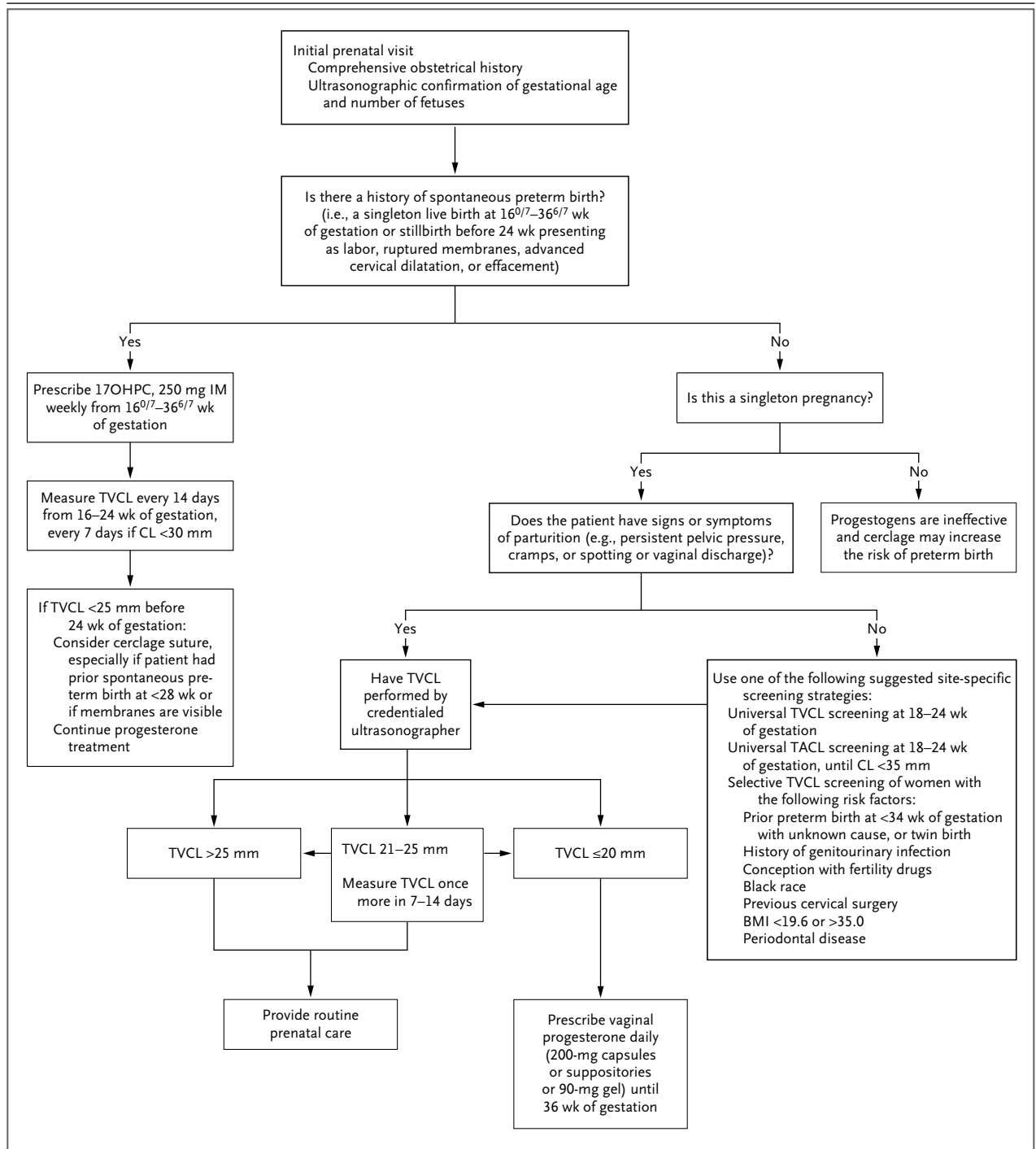
Figure 3 (facing page). Algorithm for the Screening and Treatment of Pregnant Women to Reduce the Risk of Preterm Birth.

The definition of spontaneous preterm birth includes a stillbirth before 24 weeks of gestation because many stillbirths at this gestational age represent the intrapartum death of previable neonates.^{9,10} The symptoms of parturition are symptoms of preterm cervical change, not of active labor; they may occur in normal pregnancy. Measurement of cervical length (CL) is appropriate when these symptoms persist for more than 1 day. There is no evidence-based treatment protocol for twin or triplet pregnancies. If the transvaginal cervical length (TVCL) is less than 25 mm before 24 weeks of gestation, continued treatment with 17OHPC 17 alpha-hydroxyprogesterone caproate (17OHP) is appropriate, although some experts recommend switching to vaginal progesterone when progressive cervical shortening occurs in such women. If the TVCL is 20 mm or less and there has been no previous preterm birth, the role of cervical cerclage is uncertain. The choice of suggested screening strategies depends on the population of women cared for in the practice or clinic. The risk factors associated with selective TVCL screening represent factors associated with a relative risk of preterm birth of 1.5 or more as compared with the risk in the general population of pregnant women, but the list is not prescriptive or all-inclusive. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), IM intramuscular, and TACL transabdominal cervical length. Gestation is represented in weeks^{days/7}.

Ultrasonographic screening for a short cervix is indicated for women with such symptoms as persistent pelvic pressure, cramps, spotting, and increased vaginal discharge. Progestogen treatment is recommended if the cervical length is 20 mm or less.

Prescription of Progesterone

Vaginal progesterone is available as manufactured capsules and gel and as compounded suppositories; none of these formulations are currently approved by the Food and Drug Administration (FDA) to reduce the risk of preterm birth among women with a short cervix. Manufactured (FDA-approved) and compounded 17OHP formulations are available for women who have had a previous preterm birth. FDA advisories promote manufactured products but do not proscribe compounded progesterones, which are often substantially less costly but lack the regulatory oversight required for FDA approval. The credentials and safety standards of compounding pharmacies and applicable local laws should be checked before compounded progesterones are prescribed.



In an analysis by Chang et al., compounded 17OHPC from 15 pharmacies in the United States “did not raise safety concerns when assessed for potency, sterility, pyrogen status, or impurities.”⁵⁵ Uncertainty on the part of providers about what to prescribe (e.g., which formulation and route of administration) may delay treatment. Moreover,

drug costs, questions about insurance coverage, and limited availability of certain preparations often result in an interval of days or weeks between the writing of a prescription and receipt of the medication. Nurse navigators with specialized training in progesterone treatment may be useful in overcoming these delays.

Side effects of progesterone are mainly local, such as swelling at the injection site and vaginal dryness. Women should be asked whether they have allergies to the yam, soy, or peanut base of progestogens.

lished guidelines agree on treatment, they leave open the question of how best to identify eligible women. Recommendations in this article are generally concordant with these guidelines.

AREAS OF UNCERTAINTY

The pathophysiology of preterm parturition and the basis of its association with risk factors such as black race are poorly understood. The mechanism of action of progestogens and the optimal route of administration and dose of progestogen supplementation for reducing the risk of preterm birth are also uncertain. More research is needed to identify women who give birth prematurely but do not have a short cervix and to determine the relative benefit of treatment with progestogens in women with a short cervix.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has had two early preterm births. Her risk of recurrent preterm birth is at least 35% and is higher if she is black. Her first prenatal visit should include ultrasonography to determine the number of weeks of gestation, and a careful history taking to identify other risk factors, such as cigarette smoking, nutritional deficits, and genitourinary infections (even though trials have not shown the efficacy of nutritional supplementation and treatment of genitourinary infection in reducing preterm birth rates). She should receive supplemental progestogen treatment, with either 17OHP injections or vaginal progesterone. She should also undergo regular transvaginal ultrasonographic surveillance of cervical length, beginning at 16 weeks of gestation, with consideration of cerclage if the cervix measures less than 25 mm before 24 weeks of gestation. Finally, she should be educated about the signs and symptoms of early cervical change that warrant prompt evaluation.

GUIDELINES

The Society for Maternal-Fetal Medicine⁵³ and the American College of Obstetricians and Gynecologists⁵⁴ have issued guidelines recommending that women with a previous spontaneous preterm birth be offered treatment with weekly injections of 17OHP and that women with a short cervix (≤ 20 mm) be offered treatment with vaginal progesterone. The guidelines highlight the importance of obtaining a thorough obstetrical history and the need for proper training to obtain satisfactory ultrasonographic images. Universal ultrasonographic screening is supported but not considered mandatory. Although the pub-

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