Clinical Expert Series

CME

Identification of Candidates for Progesterone
Why, Who, How, and When?

Jay D. Iams, MD

Recognition of preterm birth as the major underlying cause of infant mortality in the United States has placed responsibility for prevention in the hands of obstetrician–gynecologists. The advent of effective methods to identify and treat women with increased risk is a major advance that will alter the focus of prenatal care. Adoption of research findings into clinical practice, never an easy task, will be particularly challenging for efforts to reduce the risk of preterm birth. Historical risk factors for preterm birth are numerous and variably defined. Measurement of the length of the cervix with ultrasonography requires unique personnel and facilities. Care algorithms exist but lack the detailed information that comes with experience. This review offers perspective and detail to aid health care practitioners in developing a prematurity prevention strategy appropriate to their practice population.

Preterm birth is the underlying cause of 35% of infant deaths in the first year of life[1,2] and substantial short- and long-term morbidity in survivors.[3] More than two thirds of preterm births in developed nations occur after the spontaneous initiation of parturition before 37 weeks of gestation. Although the rate of births before 37 weeks of gestation in the United States has declined annually since 2006, to 11.5% of live births in 2012, the rate of births before 32 weeks of gestation (1.93%) has not changed significantly since 1990.[4] These early preterm births account for more than 70% of neonatal deaths and are the single largest contributor to overall infant mortality.

Methods to identify and treat women to reduce risk of preterm birth were sought unsuccessfully until recently, when reductions in spontaneous preterm birth were reported from well-designed clinical trials of pro-

From the Ohio State University Wexner Medical Center, Columbus, Ohio.

Continuing medical education for this article is available at http://links.lww.com/AOG/A496.

Corresponding author: Jay D. Iams, MD, The Ohio State University Wexner Medical Center, 395 West 12th Avenue, Columbus, OH 43210-1267; e-mail: jay.iams@osumc.edu.

gestational agents given to women with one of two major risk factors: a prior spontaneous preterm birth[5,6] or a short cervix on transvaginal ultrasonography.[7,8] Initial reports of reduced rates of preterm birth with progestogen prophylaxis were met with skepticism followed by growing excitement as successive trials reported benefit and then by controversy and confusion about the appropriate interpretation and application of the results of multiple studies. A sufficient consensus has since emerged to allow creation of treatment protocols,[9,10] but many questions remain. This report reviews areas of consensus and uncertainty and describes individual and systematic strategies to integrate screening and treatment protocols into practice.

WHY DID THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS AND THE SOCIETY FOR MATERNAL-FETAL MEDICINE ISSUE GUIDELINES IN 2012?

The importance of preterm birth as the principal unsolved problem in perinatal medicine had acquired an aura of permanence after decades of failed efforts to solve it. Two observations converged in 2012 to overcome that inertia: the weight of evidence supporting progestogen prophylaxis for at-risk women increased in 2011 with the publication by Hassan et al,[8] showing significantly reduced rates of preterm birth and perinatal morbidity in women with short cervical length 10–20 mm treated with vaginal

progesterone. This trial joined studies of vaginal progesterone that found similar reductions in preterm birth in women with short cervical length 15 mm or less[7] and in women with prior spontaneous preterm birth and other risks[5] and a trial of 17α-hydroxyprogesterone caproate[6] that reported significant reduction in preterm birth rates in women with prior spontaneous preterm birth. The contribution of preterm birth to infant mortality[1] and specifically to racial disparities in infant and perinatal mortality[11] was recognized and could no longer be ignored.

Sufficient consensus occurred in response to these publications to allow creation of guidelines by the American College of Obstetricians and Gynecologists (the College)[10] and the Society for Maternal-Fetal Medicine (SMFM).[9] Both documents recommend that women with a prior spontaneous preterm birth and short cervix be offered treatment with supplemental progestogens, but uncertainties remain about how to use these guidelines in practice. The care algorithm shown in Figure 1 is consistent with the two protocols but offers additional exposition about decision points that are uncertain.

DEFINITION OF SPONTANEOUS PRETERM BIRTH

Spontaneous preterm birth is traditionally defined as one that follows the spontaneous onset of labor or membrane rupture, but clinicians know that this definition can be difficult to apply in practice. In addition to women who meet traditional criteria for spontaneous preterm birth, there are three situations in which progestogen supplementation should also be considered: 1) women with a previous birth between 16 and 24 weeks of gestation attributed to cervical insufficiency or stillbirth have an increased likelihood of subsequent spontaneous preterm birth[12,13] and should be offered progestogen prophylaxis. Many of these births are the result of the same etiologic pathways that lead to traditionally defined spontaneous prematurity[14]; 2) when the circumstances of a potential qualifying preterm birth are unclear, eg, a birth with features of both spontaneous (ruptured membranes) and indicated (bleeding) preterm birth,[15,16] progestogen supplementation may be initiated empirically or cervical ultrasound may be used to assess risk. This latter option is supported by two studies relating the risk of recurrent preterm birth to cervical length. In an observational study of cervical length at 22–24 weeks of gestation in women with a previous preterm birth, births before 35 weeks of gestation occurred in more than 30% of women with cervical length shorter than 25 mm but in fewer than 10% among women with

cervical length 35 mm or more.[17] Another study screened 1,014 women with a history of preterm birth with serial transvaginal ultrasound measurements of cervical length between 16 and 22 weeks of gestation.[18] The risk of spontaneous preterm birth before 35 weeks of gestation rose steadily as cervical length declined below 25 mm, from 30% in women with cervical length 20–24 mm, 50% with cervical length 10–19 mm, and 90% with cervical length shorter than 10 mm. In contrast, the incidence of birth before 35 weeks of gestation was 16% in women with cervical length 25 mm or greater[19]; and 3) data to guide care for women with a prior preterm birth of twins are limited to studies that report increased risk of spontaneous singleton preterm birth in future pregnancies when the gestational age of the twin pregnancy was early, before 32 weeks of gestation.[20] Cervical ultrasonography screening might be helpful here as well.

CARE FOR WOMEN WITH A PRIOR SPONTANEOUS PRETERM BIRTH

Treatment with 17α-hydroxyprogesterone caproate from 16 to 36 weeks of gestation is commonly recommended for women with this history, but several questions arise frequently.

When Should 17α-hydroxyprogesterone Caproate Be Initiated?

Health care practitioners often ask about the gestational age at which 17α-hydroxyprogesterone caproate prophylaxis should be initiated. In the trial supporting 17α-hydroxyprogesterone caproate, prophylaxis was begun as soon as possible after enrollment between 16 and 20 weeks of gestation.[6] The use of a broader enrollment window has not been studied in rigorous trials, but descriptive reports suggest there may be benefit for early initiation of treatment and for treatment begun after 20 weeks of gestation. One clinic reported significant reduction in rates of recurrent spontaneous preterm birth in women treated with 17α-hydroxyprogesterone caproate only after the mean gestational age at first injection was reduced from 19 to 16 weeks of gestation.[21] In another, rates of preterm birth were not different in women who initiated 17α-hydroxyprogesterone caproate between 16 and 21 weeks of gestation compared with those first treated between 23 and 27 weeks of gestation.[22] Treatment of women with a short cervix of 20 mm or less with vaginal progesterone has been beneficial in women enrolled between 20 and 24 weeks of gestation.[5,7,8] These reports do not override the current 16- to 20-weeks of gestation guideline for initiation of 17α-hydroxyprogesterone caproate but suggest that
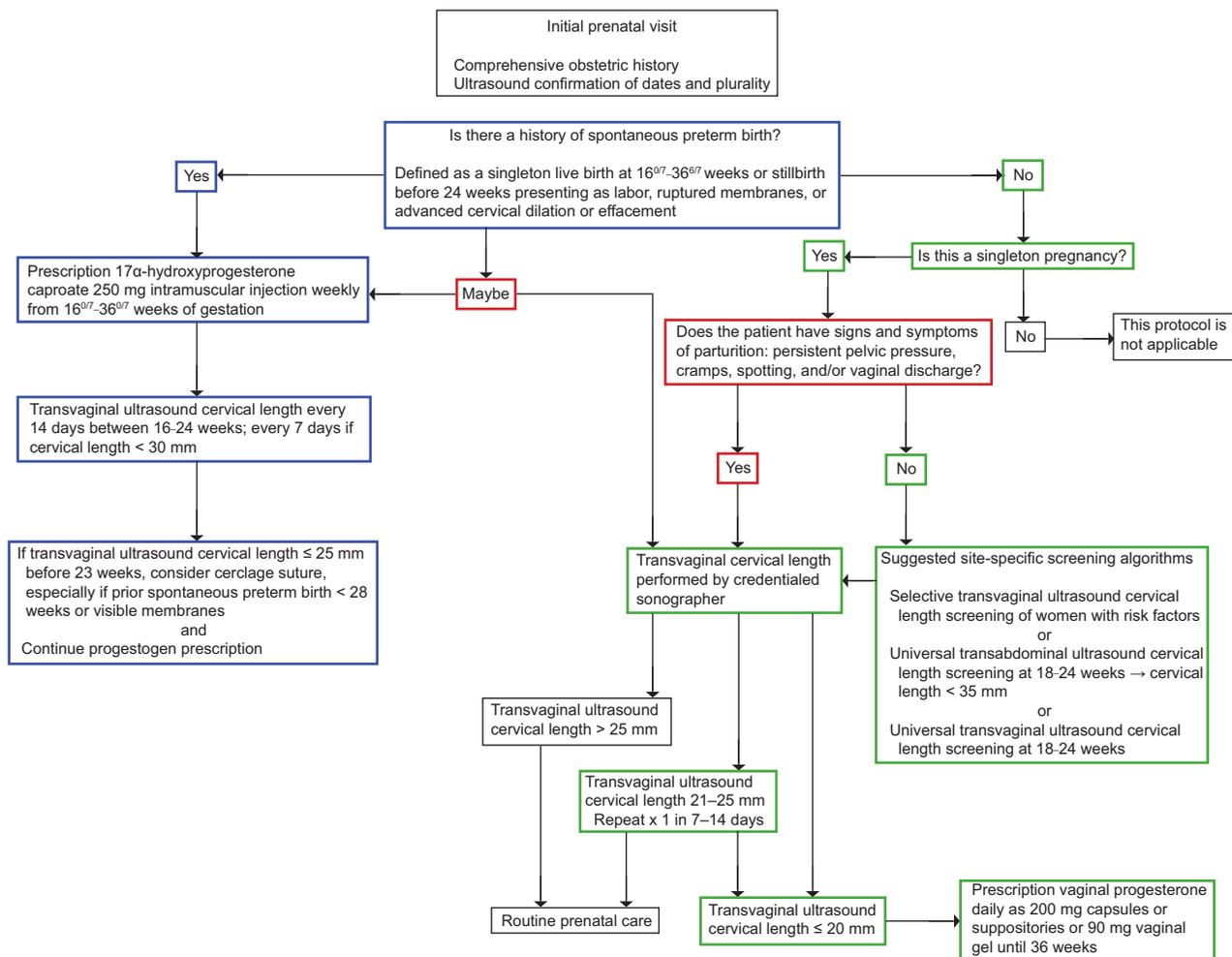
Initial prenatal visit

Comprehensive obstetric history
Ultrasound confirmation of dates and plurality

Is there a history of spontaneous preterm birth?

Defined as a singleton live birth at $16^{0/7}$–$36^{6/7}$ weeks or stillbirth before 24 weeks presenting as labor, ruptured membranes, or advanced cervical dilation or effacement

Yes

No

Maybe

Is this a singleton pregnancy?

Yes

No

Prescription 17α-hydroxyprogesterone caproate 250 mg intramuscular injection weekly from $16^{0/7}$–$36^{0/7}$ weeks of gestation

Does the patient have signs and symptoms of parturition: persistent pelvic pressure, cramps, spotting, and/or vaginal discharge?

This protocol is not applicable

Transvaginal ultrasound cervical length every 14 days between 16–24 weeks; every 7 days if cervical length < 30 mm

Yes

No

If transvaginal ultrasound cervical length ≤ 25 mm before 23 weeks, consider cerclage suture, especially if prior spontaneous preterm birth < 28 weeks or visible membranes
and
Continue progestogen prescription

Transvaginal cervical length performed by credentialed sonographer

Suggested site-specific screening algorithms

Selective transvaginal ultrasound cervical length screening of women with risk factors
or
Universal transabdominal ultrasound cervical length screening at 18–24 weeks → cervical length < 35 mm
or
Universal transvaginal ultrasound cervical length screening at 18–24 weeks

Transvaginal ultrasound cervical length > 25 mm

Transvaginal ultrasound cervical length 21–25 mm
Repeat x 1 in 7–14 days

Routine prenatal care

Transvaginal ultrasound cervical length ≤ 20 mm

Prescription vaginal progesterone daily as 200 mg capsules or suppositories or 90 mg vaginal gel until 36 weeks

Fig. 1. Care algorithm. Weeks, menstrual weeks of gestation assuming conception on 14th cycle day; BMI, body mass index; progestogen, a progestational agent demonstrated in one or more trials to prolong pregnancy, a term that includes both 17α-hydroxyprogesterone caproate and progesterone, manufactured or compounded. The *blue portion* of the figure notes comments on care of women with a previous spontaneous preterm birth. The *green portion* of the figure notes comments on screening algorithm for asymptomatic women without a prior preterm birth. The *red portion* of the figure notes comments on care of women with uncertain pregnancy histories, symptoms of cervical change, or both uncertain pregnancy histories and symptoms of cervical change. Modified from Iams JD. Prevention of preterm parturition. N Engl J Med 2014;370:254–61. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

Iams. *Identification of Candidates for Progesterone. Obstet Gynecol 2014.*

progestogen prophylaxis should be started as soon as possible after an eligible patient is identified.

What Is the Rationale for and Frequency of Cervical Ultrasound Examinations?

The rationale for periodic cervical ultrasound measurements in women receiving 17α-hydroxyprogesterone caproate derives from the improved outcomes reported for women with a prior preterm birth treated with cerclage in the National Institute of Child Health and Human Development Vaginal Ultrasound Cerclage Trial when cervical length was shorter than 25 mm before 23 weeks of gestation.[16] We begin cervical length measurements at 16 weeks of gestation and repeat them every 2 weeks thereafter, moving to weekly examinations if the length falls below 30 mm. Whether cervical length measurements can guide other treatment strategies, eg, timing of antenatal corticosteroids, to improve outcomes after 23 weeks of gestation is unknown.

Should Progestogen Treatment Be Continued in Women With Progressive Cervical Shortening Despite 17α-hydroxyprogesterone Caproate?

The answer is yes. The construct used in this review considers cervical shortening to be evidence of

preterm parturition, for which progestogen supplementation is the appropriate medical treatment regardless of obstetric history. Whether to replace 17α-hydroxyprogesterone caproate with vaginal progesterone in this situation has not been addressed in clinical trials. Women with a prior preterm birth whose cervical length falls below 25 mm are candidates for cerclage.

When Is a Cervical Cerclage Indicated in a Patient Being Treated With 17α-Hydroxyprogesterone Caproate for a Prior Spontaneous Preterm Birth?

Most follow the recommendations from a Level I meta-analysis to consider cerclage in these women when cervical length is below 25 mm.[23] Remarkably, in the Vaginal Ultrasound Cerclage Trial, the benefit of cerclage was almost entirely confined to women with cervical lengths below 15 mm.[18] The proper application of these data account for the flexibility in the algorithm shown in Figure 1. The upper gestational age limit for cerclage placement in the Vaginal Ultrasound Cerclage Trial was 23 weeks+6 days, although the majority were placed before 23 weeks of gestation.

CLINICAL INDICATIONS FOR ULTRASONOGRAPHY IN PREMATURITY PREVENTION
Prematurity Prevention for Women With Multifetal Gestation

Premature birth is the most common complication of multifetal pregnancies; half of twin and more than three fourths of triplet births occur before 37 weeks of gestation. Prevention of multifetal preterm birth is best addressed by adherence to current guidelines for fertility care that reduce the risk of multifetal conceptions.[24] Identification of multifetal pregnancies requires ultrasonography to document fetal number, determine chorionicity, and oversee fetal growth and well-being, but the value of cervical length measurement in multifetal pregnancies is uncertain. When multifetal pregnancy is recognized, there are no strategies that have been shown to reduce the incidence of preterm birth. Specifically, progesterone supplementation does not reduce the risk of preterm birth in twin or triplet pregnancies, even when the cervix is short,[25,26] and cerclage can actually increase the risk of preterm birth in women with twins and a short cervix.[27] There is insufficient evidence to support alternate methods such as pessaries[28] to reduce preterm birth in multifetal gestations.

When Is Cervical Ultrasonography Clinically Indicated in Singleton Pregnancies?

There are symptoms and signs of preterm parturition that are indications for cervical ultrasonography to detect a short cervix, especially between 16 and 24 weeks of gestation when progestogen treatment may be initiated. Symptoms suggesting preterm cervical change include persistent mild cramping similar to menses, altered vaginal discharge, pelvic pressure, backache, or a combination of these.[29] Painful contractions are not a prominent symptom of early cervical change, because the magnitude of contraction-related pain is inversely related to the duration and degree of cervical ripening that preceded contractions.[30] Such symptoms may be normal if transient in the second and third trimesters, but their persistence for more than 24 hours is clinically significant. Spotting and fluid leakage are abnormal in the second trimester.

PRETERM BIRTH PREVENTION IN ROUTINE PRENATAL CARE
What Cervical Length Screening Strategy Should Be Adopted for Asymptomatic Women With No History of Preterm Birth?

Now that treatment is available for a significant proportion of the population at risk for preterm birth, obstetricians have an opportunity and responsibility to address the leading underlying cause of infant death.[1] For this reason, Stuart Campbell, the Father of Obstetric Ultrasound, declared that "Doing nothing is no longer an option."[31] However, what to do? The guidelines issued by the College and the SMFM leave open the question of whether an individual practice group, clinic, or hospital should adopt universal cervical length screening at 18–24 weeks of gestation for all prenatal patients. However, the guidelines advise prenatal caregivers in all settings to screen their patients for preterm birth risk by clinical history accompanied by a practice-specific algorithm to identify women who are candidates for transvaginal cervical ultrasonography. Optimal application of these advisories in practice will vary according to the risk of preterm birth in the population served and the availability of equipment and personnel. None of the strategies in Figure 1 has been tested in practice when linked to any form of progestogen supplementation, and all have limitations. Because universal transvaginal ultrasonography at 18–24 weeks of gestation to measure cervical length may require significant revisions to routine practice, strategies to reduce the number of women who undergo transvaginal

ultrasonography have been sought. This might be accomplished by limiting transvaginal cervical length screening to women with one or more clinical risk factors (screening in) or by excluding women with a reassuring cervical length measured on a transabdominal ultrasonogram or a similarly reassuring obstetric history (screening out).

Selective Transvaginal Ultrasonography Screening of Women With Risk Factors for Spontaneous Preterm Birth (Screening In)

When considered as potential indications for selective cervical length screening, the prevalence and diversity of risk factors associated with preterm birth risk are daunting. Risk factors are numerous and many are controversial. Attempts to create a list or scoring system of risk factors that could identify women at risk for preterm birth have been largely unsuccessful.[32] Whether a short cervix is more common among women with traditional risk factors for spontaneous preterm birth has not been well-studied but is suggested by variable rates of a short cervix across populations. Risk factors associated with an increased risk of spontaneous preterm birth include a history of cervical procedures,[33,34] sexually transmitted infections,[35,36] extremes of prepregnancy weight (body mass index [calculated as weight (kg)/[height (m)]^2] less than 19.8 or greater than 35),[35] periodontal disease,[35] assisted conception,[24,37,38] and a family history of preterm birth.[39] Notably, rates of preterm birth are almost twofold higher among black (African American and Afro-Caribbean) women (16–18%) than among Asian, Hispanic, and white women in the United States[40] and remain higher after controlling for social disadvantage and education.[41,42] Attempts to predict preterm birth by combining clinical and demographic risk factors with cervical length have had mixed results. Although successful in one study,[43] a useful model to predict spontaneous preterm birth could not be developed using demographic and ultrasound findings from a large multicenter study of nulliparous women screened for a short cervix.[44]

Universal Transabdominal Cervical Ultrasonography to Identify Women With Low Risk of a Short Cervix and Spontaneous Preterm Birth (Screening Out)

Another path to limit the number of women who are candidates for transvaginal ultrasonography would be to identify a population of women who are very unlikely to have a short cervix or preterm birth. This approach could be explored by considering women with reassuring obstetric histories, eg, women whose previous pregnancies have all reached term (risk in this group is 5%)[45] or by performing a preliminary transabdominal ultrasound examination to find women with a very low likelihood of a short cervix. The latter approach was examined in a study of 1,217 women who underwent both transabdominal and transvaginal ultrasonography to measure cervical length.[46] Although an acceptable transabdominal image of the cervix could not be obtained in 6%, a prevoid transabdominal cervical length 35 mm or less had 100% sensitivity to detect transvaginal cervical lengths 20 mm or less with 41% specificity. If replicated in other centers, this approach might safely reduce the need for the time, equipment, and personnel required for transvaginal ultrasonography in as many as 40% of pregnancies. However, others have not found transabdominal imaging of the cervix to be sensitive to detect short cervix,[47] and a cost-effectiveness comparison of transabdominal prescreening to universal transvaginal screening found the latter was superior.[48]

Historical screening out is also not fully reassuring; although a short cervix is less common in women without risk factors, if a short cervix is present, it confers a similarly increased relative risk of preterm birth in nulliparous women and women whose prior birth was at term.[49]

Universal Transvaginal Ultrasound Screening of Asymptomatic Women

Offering transvaginal ultrasonography to measure cervical length in all pregnant women during a second-trimester visit to assess fetal anatomy using ultrasound is supported as an option in both the College and SMFM statements. The advantage of this approach is optimal sensitivity to detect a treatable condition that may not otherwise be discovered and that accounts for a substantial fraction of preterm birth. The disadvantages lie in the details of creating a cost-effective, efficient, and accurate system to perform these examinations. The College Practice Bulletin[10] notes that although progestogen supplementation "…has the potential to reduce the preterm birth rate…" "…and is cost effective, safe, accepted by patients, and widely available," it also cautions that universal application of cervical length screening raises concerns about "…quality assurance of (transvaginal cervical ultrasonography)…" "…and the potential for patients to receive unnecessary or unproven interventions"[10] as might occur in women with marginal (21–25 mm) cervical length screening measurements (see subsequent paragraph about caring for these women).

Quality Assurance

An improperly performed transvaginal ultrasound measurement of cervical length could lead to unneeded treatment or become a missed opportunity to prevent a preterm birth. To achieve reduced rates of preterm birth, cervical ultrasonography will have to be performed by credentialed ultrasonographers who devote adequate time to generating images using appropriate technique and equipment. Training and adherence to standard imaging and measurement criteria have been shown to improve the reproducibility of the examination.[50] In a study of ultrasonographers seeking credentials to perform cervical ultrasonography in a research protocol, adherence to these criteria was good (83%) but not optimal for a test that might be offered to all pregnant women.[51] The training, credentials, and performance of persons currently performing transvaginal cervical ultrasonography are uncertain but thought to be variable. Education in the principles and practice of transvaginal ultrasonography to measure the cervix are available online without cost from the Fetal Medicine Foundation[52] and from Cervical Length Education and Review,[53] a credentialing program sponsored by the College, the SMFM, the American College of Osteopathic Obstetricians & Gynecologists, the American College of Radiology, and the American Institute of Ultrasound in Medicine. The Fetal Medicine Foundation offers image review and credentialing without cost; Cervical Length Education and Review offers image review, continuing education credits, and credentialing for a combined fee of $150.

The availability of transvaginal ultrasonography will likely vary geographically by population density and incidence of preterm birth. Experience over time will determine whether the frequency of screen-positive women varies according to geographic and demographic characteristics. The present situation may prove to be similar to the experience with screening and prophylaxis of group B streptococcal infection where optimal strategies became evident only after they were adopted on a large scale in various populations, only to yield unexpected long-term effects. Until such data are available, clinicians are challenged to choose something more active than serendipitous identification of women with an indication for progesterone prophylaxis.

APPLICATION OF PREMATURITY SCREENING PROTOCOLS

One of the barriers to successful application of cervical length screening, and certainly the one most likely to cause controversy, is variable interpretation of the published protocols in clinical practice. This phenomenon is not new for College Practice Bulletins; the recent emphasis by the College and other organizations on greater adherence to a 1999 College Practice Bulletin (No. 10, now replaced by No. 107[54]) about indications for scheduled birth before 39 weeks of gestation is an example. Because the progestogen and cervical length protocols are relatively new, variable interpretations may occur in several areas.

What Is the Threshold Cervical Length to Initiate Progestogens?

The threshold cervical length to initiate progesterone treatment in College and SMFM protocols is 20 mm. The 20-mm threshold is supported not only by the two largest trials showing benefit for vaginal progesterone[7,8] for women who met this criterion, but also by two trials, one with vaginal progesterone and the other with 17α-hydroxyprogesterone caproate, which failed to show benefit of progestogen treatment in women whose cervical length measurements were greater than 20 mm. Vaginal progesterone did not reduce preterm birth in a trial that enrolled 611 women with a prior preterm birth, only 25 of whom (4%) had a cervical length less than 25 mm (mean cervical length 37 mm).[55] Also, 17α-hydroxyprogesterone caproate did not reduce rates of preterm birth in a trial that enrolled 657 nulliparous women with cervical length below 30 mm, 542 (82%) of whom had a cervical length greater than 20 mm.[56] These data support a threshold of 20 mm or shorter to initiate progestogen treatment.

What Strategy Should be Used in Caring for Women With a Marginal Cervical Length Screening Measurement (21–25 mm)?

Despite the abundance of data supporting a 20-mm threshold, there are no data to guide management for women whose cervical length is just above the threshold. Studies of the rate of progressive cervical shortening not surprisingly show greater risk of preterm birth in women with higher rate of shortening,[57] but this has not been used to guide treatment. Clinicians should recognize that "indication creep," expansion of the definition or threshold for treatment, is a common phenomenon with any care algorithm that always carries risks and costs. Until further information is available, the course used in our clinic when the initial cervical length measurement is 21–25 mm is to review the obstetric history for risk factors, and, finding none, schedule a single automatic second measurement in 7–14 days. Women with stable cervical

length above 20 mm are reassured that treatment is not helpful[55,56] and advised to report persistent symptoms.

Is There a Role for Cerclage in Women With a Short Cervix Who Do Not Have a Prior Second-Trimester Delivery?

The answer is currently "no." There is no evidence to support this practice, and we do not offer cerclage to women with this clinical picture. However, the question challenges traditional historical criteria for cervical insufficiency: painless cervical dilation, leading to recurrent births in the second-trimester in the absence of other causes. These criteria were once believed to identify women whose early births were caused solely by structural weakness of cervical tissue that could be corrected by surgical repair. However, the success of medical (progestogen) treatment for short cervix in women who meet these criteria[7,8] and the observation that cerclage is more effective in women with a very short cervix (15 mm or less) than for those with cervical length 16–25 mm[18] together suggest that most women who carry this diagnosis do not in fact have a structural deficit. If a short cervix is an indication that preterm parturition has begun, medical treatment with progesterone is the proven therapy. However, it is possible that future studies will demonstrate that if shortening progresses below a yet-to-be determined threshold or rate of change in women without a prior second trimester birth, progesterone therapy should be supplemented by surgical (cerclage) treatment.

What Formulation(s) of Progestogens Should Be Used?

Although 17α-hydroxyprogesterone caproate is the progestogen commonly prescribed for women with a prior spontaneous preterm birth and vaginal progesterone for women with a short cervix 20 mm or less, there are numerous issues and uncertainties that affect clinical practice. The answers are related to how the literature is interpreted and to how 17α-hydroxyprogesterone caproate and vaginal progesterone are made available to our patients.

The Literature

The algorithms prepared by the College and the SMFM share a common application of the results of research trials to clinical practice: 17α-hydroxyprogesterone caproate reduced the incidence of spontaneous preterm birth in women with a prior spontaneous preterm birth[6]; vaginal progesterone did not.[55] Vaginal progesterone reduced the incidence of spontaneous preterm birth in women with a short cervix[7,8]; 17α-hydroxyprogesterone caproate did not.[56] The SMFM and College algorithms are consistent with these results, but a more nuanced interpretation arises when treatment trials are considered together with the cervical ultrasonography literature cited previously. When the trials were designed, a prior preterm birth and short cervix were considered to be independent methods of identifying women with increased risk, but they are not. The risk of recurrent preterm birth varies substantially according to cervical length measured at 22–24 weeks of gestation in the next pregnancy. In an observational study of masked cervical length measurements at 22–24 weeks of gestation in women with a prior preterm birth, the risk of recurrent preterm birth before 35 weeks of gestation was 8% in women whose cervical length was longer than 35 mm, 16% if the cervical length was 25–35 mm, and 30% in women with a cervical length shorter than 25 mm.[17] In another study of women with a prior spontaneous preterm birth, the rate of repeat preterm birth was 45% in the 30% of enrollees with a cervix that measured less than 25 mm before 24 weeks of gestation compared with 16% among the 70% whose cervical length was 25 mm or greater.[18,19] Vaginal progesterone did not reduce preterm birth in a trial that enrolled women with a prior preterm birth whose cervical length at entry was normal (mean 37 mm; only 4% had cervical length shorter than 25 mm),[55] and 17α-hydroxyprogesterone caproate did not reduce rates of preterm birth in a trial that enrolled 657 nulliparous women with cervical length below 30 mm, 56 (8.5%) of whom had a cervical length shorter than 15 mm.[56] Although cervical length was not measured in the largest trial of 17α-hydroxyprogesterone caproate,[6] the women enrolled had characteristics associated with a short cervix: the mean gestational age of the qualifying birth was 31 weeks, and 32% had more than one previous preterm birth.[58] These observations about the relation between cervical length and recurrence of preterm birth suggest that it is a short cervix that is the indication for progestogen prophylaxis and that a history of a prior preterm birth identifies a population that should undergo cervical length measurement. This is the rationale used in our clinic to care for women with a history of preterm birth that is uncertain, eg, suggestive of abruption, or complicated by multiple factors. We offer 17α-hydroxyprogesterone caproate to these patients and follow those who decline with cervical ultrasonography every 2 weeks between 16 and 24 weeks of gestation; progestogen therapy is recommended, using a higher 25-mm threshold, if a short cervix is identified before 24 weeks of gestation.

PRESCRIBING PROGESTERONE

Provision of progestogen preparations to eligible women has been complicated by the various interpretations of the literature described, but even more so by controversies surrounding the preparation (compounding for individual patients compared with manufactured), cost, and safety of various progestational agents. There are six preparations available for prescription, listed here (Table 1), prepared for use in the Prematurity Clinic at Ohio State that displays relative cost estimates that represent the wide variation in the cost of treatment.

The safety of compounded compared with manufactured pharmaceuticals has been the subject of media attention because of unsafe practices by specific pharmacies that provided compounded glucocorticoids. No such violations have been reported for pharmacies that provide compounded progestational agents, but physicians should be aware of statements by the U.S. Food and Drug Administration (FDA) regarding manufactured and compounded hydroxyprogesterone caproate (see FDA's Questions and Answers on Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm310215.htm).

Laws regulating compounding pharmacies vary by state. Physicians who prescribe compounded progestational agents should ask the compounding pharmacies to describe their credentials and safety standards.

Other safety issues surrounding progestational agents include concerns about potential allergies to the yam, soy, or peanut base used in manufacturing or compounding. Finally, there is a theoretical concern about the safety of prolonging pregnancy when the cause of preterm parturition, eg, intrauterine inflammation or decidual bleeding may have an adverse effect on the fetus. Although these concerns are appropriate, and fetal well-being should always be reviewed, information available about the health of newborns, infants, and children exposed in utero to progestational treatment to prolong pregnancy has been reassuring.[59,60]

CONCLUSION

Obstetrician–gynecologists are now charged with a new responsibility to reduce infant mortality by making prevention of prematurity a routine part of

Table 1. Relative Costs of Progestogens Shown in Amounts Commonly Provided

Form	Source	Supplied As	$/Supplied	$/Dose	$/Wk	$/Mo
Compounded 17α-hydroxyprogesterone caproate		250 mg/mL				
	Local	5-mL vial	$$/5 mL	$	$	$$
	Alere	5-mL vial	Varies	Varies	Varies	Varies
	National	5-mL vial	$$/5 mL	$	$	$$
		10-mL vial	$$$/10 mL	$	$	$$
Manufactured 17α-hydroxyprogesterone caproate	Ther-Rx	Per injection				
		No insurance or less than $60,000/y	0	0	0	0
		No insurance or greater than $60,000/y	0–$	0–$	0–$	0 -$$
		Insurance or less than $120,000/y	$	$	$	$$
		Insurance or greater than $120,000/y	$$	$$	$$	$$$–$$$$
Vaginal progesterone						
Compounded suppository*	Local	30/200 mg	$$	$	$	$$
	National	30/200 mg	$$	$	$	$$
Capsule						
Prometrium*		30/200 mg	$$	$	$	$$
Gel						
Prochieve		1.4 g/90 mg	$$	$$	$$$	$$$$
Crinone		1 g/90 mg	$$$$	$	$$$	$$$$

$, $20.00 or less; $$, $20–90; $$$, $100–290; $$$$, $300–1,000 or more.
* Potential allergic reactions may occur. Compounded vaginal progesterone suppositories are yam-based or soy-based. Vaginal progesterone capsules contain peanut oil.

care for every pregnancy. Risk factors for preterm birth amenable to progestogens should be identified at the first prenatal visit to allow time to overcome systemic barriers to initiation of prophylaxis. Practices and clinics would be wise to adopt a plan to identify women eligible for cervical ultrasound screening that is appropriate to their population and work with payers, pharmacies, and hospitals to assure its efficient application.

REFERENCES

1. Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics 2006;118:1566–73.

2. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2009 period linked birth/infant death data set. National Vital Statistics Report; vol. 60, no. 5. Hyattsville (MD): National Center for Health Statistics; 2013.

3. Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. BMJ 2012;344:e896.

4. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ. Births: final data for 2012. National Vital Statistics Reports; vol. 62, no. 9. Hyattsville (MD): National Center for Health Statistics; 2013.

5. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib 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.

6. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17-alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.

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

8. 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, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18–31.

9. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol 2012;206:376–86. Erratum in Am J Obstet Gynecol 2013;208:86.

10. American College of Obstetricians and Gynecologists. Prediction and prevention of preterm birth. Practice Bulletin No. 130. Obstet Gynecol 2012;120:964–73.

11. Spong CY, Iams J, Goldenberg R, Hauck FR, Willinger M. Disparities in perinatal medicine: preterm birth, stillbirth, and infant mortality. Obstet Gynecol 2011;117:948–55.

12. Edlow AG, Srinivas SK, Elovitz MA. Second trimester loss and subsequent pregnancy outcomes: what is the real risk? Am J Obstet Gynecol 2007;197:581.e1–6.

13. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. JAMA 2011;306:2459–68.

14. Silver RM, Branch DW, Goldenberg R, Iams JD, Klebanoff MA. Nomenclature for pregnancy outcomes: time for a change. Obstet Gynecol 2011;118:1402–8.

15. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous vs. medically-indicated preterm birth. Am J Obstet Gynecol 2006;195:643–50.

16. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol 2014;210:131.e1–8.

17. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. Am J Obstet Gynecol 1998;178:1035–40.

18. Owen J, Hankins G, Iams JD, Berghella V, Sheffield JS, Perez-Delboy A, et al. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. Am J Obstet Gynecol 2009;201:375.e1–8.

19. Owen J, Szychowski JM, Hankins G, Iams JD, Sheffield JS, Perez-Delboy A, et al. Cervical lengths above 25 mm and preterm birth. Am J Obstet Gynecol 2010;203:393.e1–5.

20. Schaaf JM, Hof MH, Mol BW, Abu-Hanna A, Ravelli AC. Recurrence risk of preterm birth in subsequent singleton pregnancy after preterm twin delivery. Am J Obstet Gynecol 2012;207:279 e1–7.

21. Markham K, Walker H, Lynch CD, Iams JD. Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis. Obstet Gynecol 2014;123:34–9.

22. How HY, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol 2007;197:260.e1–4.

23. Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. Obstet Gynecol 2011;117:663–71.

24. Practice Committee of the American Society for Reproductive Medicine. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Fertil Steril 2012;97:825–34.

25. Senat MV, Porcher R, Winer N, Vayssière C, Deruelle P, Capelle M, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol 2013;208:194.e1–8.

26. Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. Ultrasound Obstet Gynecol 2011;38:281–7.

27. Berghella V, Odibo AO, To MS. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data, Obstet Gynecol 2005;106:181–9.

28. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013;382:1341–9.

29. Iams JD, Johnson FF, Parker M. A prospective evaluation of the signs and symptoms of preterm labor. Obstet Gynecol 1994;84:227–30.

30. Oláh KS, Gee H. The prevention of preterm delivery–can we afford to continue to ignore the cervix? Br J Obstet Gynaecol 1992;99:278–80.

31. Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving: doing nothing is no longer an option. Ultrasound Obstet Gynecol 2011;38:1–9.

32. Honest H, Bachmann LM, Sundaram R, Gupta JK, Kleijnen J, Khan KS. The accuracy of risk scores in predicting preterm birth–a systematic review. J Obstet Gynaecol 2004;24:343–59.

33. Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2007;109:309–13.

34. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. BJOG 2011;118:1031–41.

35. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.

36. Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, et al Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. N Engl J Med 2000;342:534–40.

37. American College of Obstetricians and Gynecologists. Perinatal risks associated with assisted reproductive technology. ACOG Committee Opinion No. 324. Obstet Gynecol 2005;106:1143–6.

38. McDonald SD, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis. J Obstet Gynaecol Can 2005;27:449–59.

39. Ward K, Argyle V, Meade M, Nelson L. The heritability of preterm delivery. Obstet Gynecol 2005;106:1235–9.

40. Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Mathews TJ. Births: final data for 2011. National Vital Statistics Reports; vol. 62, no. 1. Hyattsville (MD): National Center for Health Statistics; 2013.

41. Behrman RE, Stith Butler A; Committee on understanding premature birth and assuring healthy outcomes. Causes, consequences, and prevention. Washington (DC): National Academies Press; 2007.

42. Healy AJ, Malone FD, Sullivan LM, Porter TF, Luthy DA, Comstock CH, et al. Early access to prenatal care: implications for racial disparity in perinatal mortality. Obstet Gynecol 2006; 107:625–31.

43. To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound Obstet Gynecol 2006;27:362–7.

44. Grobman W. Prediction of spontaneous preterm birth among nulliparous women with a short cervix. Am J Obstet Gynecol 2014;210:128.e1–e6. SMFM Abstr 732. S358.

45. McManemy J, Cooke E, Amon E, Leet T. Recurrence risk for preterm delivery. Am J Obstet Gynecol 2007;196:576.e1–6.

46. Friedman AM, Srinivas SK, Parry S, Elovitz MA, Wang E, Schwartz N. Can transabdominal ultrasound be used as a screening test for short cervical length? Am J Obstet Gynecol 2013;208:190.e1–7.

47. To MS, Skentou C, Cicero S, Nicolaides KH. Cervical assessment at the routine 23-weeks' scan: problems with transabdominal sonography. Ultrasound Obstet Gynecol 2000;15: 292–6.

48. Miller ES, Grobman WA. Cost-effectiveness of transabdominal ultrasound for cervical length screening for preterm birth prevention. Am J Obstet Gynecol 2013;209:546.e1–6.

49. Facco FL, Simhan HN. Short ultrasonographic cervical length in women with low risk obstetric history. Obstet Gynecol 2013; 122:858–62.

50. Burger M, Weber-Rössler T, Willmann M. Measurement of the pregnant cervix by transvaginal sonography: an interobserver study and new standards to improve the interobserver variability. Ultrasound Obstet Gynecol 1997;9:188–93.

51. Iams JD, Grobman WA, Lozitska A, Spong CY, Saade G, Mercer BM, et al. Adherence to criteria for transvaginal ultrasound imaging and measurement of cervical length. Am J Obstet Gynecol 2013;209:365.e1–5.

52. Fetal Medicine Foundation. Available at: http://www.fetalmedicine.com/fmf/training-certification/certificates-of-competence/cervical-assessment/. Retrieved on April 9, 2014.

53. Cervical Length Education and Review (CLEaR) Perinatal Quality Foundation. Available at: https://clear.perinatalquality.org/. Retrieved on April 9, 2014.

54. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin No. 107. Obstet Gynecol 2009;114:386–97.

55. 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 Obstet Gynecol 2007;30:687–96.

56. Grobman WA, Thom EA, Spong CY, Iams JD, Saade GR, Mercer BM, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. Am J Obstet Gynecol 2012;207:390.e1–8.

57. Moroz LA, Simhan HN. Rate of sonographic cervical shortening and the risk of spontaneous preterm birth. Am J Obstet Gynecol 2012;206:234.e1–5.

58. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Hoawad AH, Cooper RL, et al. The preterm prediction study: the value of new vs. standard risk factors in predicting early and all spontaneous preterm births. Am J Public Health 1998;88:233–8.

59. Northen AT, Norman GS, Anderson K, Moseley L, DiVito M, Cotroneo M, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol 2007;110:865–72.

60. Meis PJ; Society for Maternal-Fetal Medicine. 17 hydroxyprogesterone for the prevention of preterm delivery. Obstet Gynecol 2005;105:1128–35.