Assessing preterm birth risk: from bulletin to bedside

Weighing in on the key messages from ACOG's recent Practice Bulletin, Errol Norwitz, MD, PhD, reviews the evidence on the utility of preterm birth screening modalities, including cervical ultrasound, fetal fibronectin, salivary estriol, and home uterine-activity monitoring.

In much of medicine, the ability to identify which patients are at increased risk for a disease or health-threatening event is half the battle, as it paves the way for timely preventive intervention. As obstetricians know all too well, however, that's hardly the case with preterm delivery (PTD). While recent years have seen significant advances in screening modalities, those gains have not been matched by comparable improvements in our ability to prevent premature birth. In fact, instead of decreasing, the incidence of PTD in the United States has increased from 9.4% of births in 1981 to 11.8% in 1999.[1]

While the search for effective interventions continues, obstetricians and their patients still can derive considerable benefit from the enhanced ability to determine which women with worrisome symptoms are at low risk of PTD, thus avoiding costly and potentially harmful interventions, and which patients warrant heightened surveillance.

In October 2001, ACOG reviewed various modalities in its Practice Bulletin titled "Assessment of risk for preterm birth." Here, Dr. Norwitz, assistant professor of obstetrics, gynecology, and reproductive sciences at Harvard Medical School and an attending Ob/Gyn in the division of maternal-fetal medicine at Brigham and Women's Hospital in Boston, responds to OBG MANAGEMENT editors' questions about the clinical implications of the bulletin and the screens and tests it discusses.

Q OBG MANAGEMENT: In what ways does this bulletin represent an evolution in the specialty's thinking about preterm labor?

A NORWITZ: It represents an attempt by ACOG to synthesize the extensive and rapidly expanding body of literature on risk factors for PTD into a single, succinct, and practical document.[2] As such, it replaces prior ACOG publications on preterm labor,[3] home uterine-activity monitoring (HUAM),[4] salivary estriol testing,[5] fetal fibronectin (fFN) testing,[6] and bacterial vaginosis (BV) screening and treatment.[7] However, the current Practice Bulletin is a far less ambitious document than the prior review of preterm labor,[3] which dealt not only with risk factors for preterm birth, but also with its management.

Nonetheless, it represents an evolution in thinking about preterm birth, as it includes a detailed discussion of fetal fibronectin screening and sonographic assessment of cervical length.

Q OBG MANAGEMENT: According to the bulletin, "There are no current data to support the use of salivary estriol, HUAM, or BV screening as strategies to identify or prevent preterm birth." How widely are each of these modalities being employed by Ob/Gyns? What impact do you see this statement having on their future use?

A NORWITZ: HUAM testing had largely fallen

by the wayside even before this bulletin was published. Most obstetric-care providers were already aware of the extensive literature showing that HUAM does not prevent preterm birth or improve perinatal outcome.[8-11]

As for salivary estriol, the development of a reliable endocrine assay to predict PTD would represent a significant advance in the field. Progesterone withdrawal is not a prerequisite for labor; nor are serum progesterone levels or progesterone/17ß-estradiol ratios predictive of preterm birth.[121]

On the other hand, maternal serum estriol levels accurately reflect activation of the fetal hypothalamic-pituitary-adrenal axis, which occurs in all women prior to the onset of labor, both at term and preterm.[13,14] Moreover, salivary estriol measurements correlate well with levels of biologically active (unconjugated) estriol in the circulation.[15] The detection of elevated levels of estriol (≥2.1 ng/mL) in maternal saliva is predictive of delivery prior to 37 weeks in a high-risk population, with a sensitivity of 68% to 87% and a specificity of 77%.[16,17] Serial (weekly) measurements have been shown to be more accurate in predicting preterm birth than a single measurement.[17]

Lower-genital-tract BV may be a marker of upper-genital-tract infection, which in turn may be the real cause of preterm birth.

However, salivary estriol testing to identify women at high risk of PTD has not been widely accepted. The reasons: First, maternal estriol levels show diurnal variation, peaking at night,[18] making it difficult to standardize such testing. Additionally, the false-positive rate of 23% to 35% is considered unacceptably high and may lead to unnecessary intervention.[16,17] Finally, salivary estriol levels may be suppressed by betamethasone administration, making the test unreliable in patients treated with corticosteroids.[19] The statement in the latest ACOG bulletin that "trials with salivary estriol testing to predict preterm birth have failed to establish its usefulness for anything more than investigational purposes at present"[2] is

likely to further limit the use of this test, and may have the unfortunate effect of discouraging future research in the field.

In regard to BV, recent data demonstrate conclusively that screening and treating low-risk asymptomatic pregnant women for BV does not prevent preterm birth.[20-22] However, the data for women at high risk for preterm birth are conflicting. Some studies suggest that the strategy of screening and treating asymptomatic BV in high-risk women may significantly decrease the incidence of preterm birth and low-birthweight infants.[22-24] But the statement by ACOG that "there are insufficient data to suggest screening and treating women at...high risk will reduce the overall rate of preterm birth"[2] is likely to limit the use of this strategy. The hypothesis that lower-genital-tract BV may be a marker of upper-genital-tract infection, which in turn is the real cause of preterm labor and delivery, is intriguing and deserves further attention.

The preventive strategy of screening and treating BV should not be confused with the management of women with symptomatic BV. These women should be treated with oral metronidazole after the first trimester, as vaginal metronidazole and clindamycin preparations appear to be less effective during pregnancy.[25]

Q OBG MANAGEMENT: The Practice Bulletin also stated that, "Screening for risk of preterm labor by means other than historic risk factors is not beneficial in the general obstetric population." Please outline this set of historic risk factors.

A NORWITZ: Risk factors for preterm birth resulting from spontaneous preterm labor, which excludes indicated (iatrogenic) PTD for severe preeclampsia, a prior high vertical ("classical") cesarean, or chorioamnionitis, are as follows:

- Demographic characteristics such as African-American race, poor socioeconomic status, low pre-pregnancy weight, extremes of maternal age, and absent or inadequate prenatal care.
- Behavioral factors such as cigarette smoking, substance abuse, and high personal stress or a strenuous work environment.
- Aspects of obstetric history such as prior PTD, multiple gestation, uterine anomalies, anemia, polyhydramnios, vaginal bleeding, cervical incompetence, and BV.

Several scoring systems have been developed to predict a woman's likelihood of delivering preterm. However, reliance on risk factors alone will fail to identify more than 50% of pregnancies that deliver at less than 37 weeks.[26,27]

The most important risk factor is a history of one or more preterm deliveries. If the prior PTD was due to spontaneous preterm labor, a screening strategy comprised of serial cervical examinations and/or fFN testing should be initiated in the mid- to late second trimester.

If the prior PTD is suggestive of cervical incompetence, it may be appropriate to discuss other management options. These include prophylactic cervical cerclage or serial measurements of cervical length using transvaginal sonography and placement of an emergent cerclage, if indicated.[28] (The generally accepted definition of cervical incompetence is the inability to support a pregnancy to term due to a structural or functional defect of the cervix. It is characterized by acute, painless dilatation of the cervix, usually in the middle trimester, culminating in prolapse and/or rupture of the membranes, which leads to preterm—and often pre-viable—delivery.) A history of in utero diethylstilbestrol (DES) exposure or multiple gestation in the absence of a history of cervical incompetence is not generally accepted as a sufficient indication for elective cerclage.[28]

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Sonography has shown a strong correlation between cervical length and PTD.

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OBG MANAGEMENT: What about fFN testing and the use of ultrasound to determine cervical length? The ACOG Practice Bulletin recommended that either modality or "a combination of both may be useful in determining high risk for preterm labor," adding that the clinical utility of both modalities may rest primarily with their negative predictive value. How do you use cervical ultrasound and fFN screening in your practice?

NORWITZ: In women at risk for preterm birth, serial digital evaluation of the cervix starting in the mid- to late second trimester is useful if the examination remains normal. However, an abnormal cervical finding (shortening, dilatation, or both) is associated with PTD in only 4% of low-risk women and in just 12% to 20% of high-risk women.[29] Real-time sonographic evaluation of the cervix, on the other hand, has demonstrated a strong and reproducible inverse correlation between cervical length and PTD.[30,31] If the cervical length is lower than the 10th percentile for gestational age, the pregnancy is at a 6-fold increased risk of delivery prior to 35 weeks.[30] A cervical length of 15 mm or less at 23 weeks occurs in less than 2% of low-risk women, but is predictive of delivery prior to 28 weeks and 32 weeks in 60% and 90% of cases, respectively.[31]

A cervical length of 2.5 cm or less at 22 to 24 weeks in a pregnancy at high risk for PTD should be considered abnormal and requires further evaluation.

The latest Practice Bulletin concludes that: "Despite the usefulness of cervical length determination by ultrasonography as a predictor of preterm labor, routine use is not recommended because of the lack of proven treatments affecting outcome."[2,32] Therefore, perinatologists and sonographers should not include cervical-length measurements in routine prenatal ultrasounds. However, in carefully selected women at increased risk for PTD, serial measurements of cervical length may help modify the risk estimate for preterm birth. This is especially true in women with a history suggestive of cervical incompetence in whom cervical cerclage is being considered. That said, it remains unclear whether placement of a cervical cerclage in women with a shortened cervix can prevent preterm birth or improve perinatal outcome.[28]

Cervical-length measurement as a screening test for preterm birth was accepted relatively quickly in clinical practice. This is likely because of the ready availability of transvaginal ultrasound in most obstetric suites and labor and delivery (L&D) units, and because of a high level of comfort and expertise with its use. The possibility that a shortened cervix may represent cervical incompetence and that placement of a cervical cerclage may serve to avert PTD altogether or at least delay delivery to a more favorable gestational age, also may be a factor in that acceptance.

Obstetric-care providers have been far more skeptical about fFN testing, and its introduction into clinical practice has been more protracted. An elevated level of fFN (≥50 ng/mL) in cervicovaginal secretions, which probably reflects separation of the fetal membranes from the maternal decidua,[33] is associated with premature delivery. However, in a low-risk population, the positive predictive value of a positive fFN test at 22 to 24 weeks for spontaneous PTD prior to 28 weeks and 37 weeks is only 13% and 36%, respectively.[34] As such, the value of this test lies primarily in its negative predictive value; 99% of patients with a negative fFN test will not deliver within 7 days.[35] ACOG currently recommends the use of this test only in a very specific subgroup of women (particularly, in symptomatic women with intact membranes, cervical dilatation <3 cm, and a gestational age of 24-0/7 to 34-6/7 weeks).[2,6]

Cervicovaginal swabs for fFN measurement should be taken prior to bimanual examination. For this reason, the clinician should consider collecting a specimen at the time of initial speculum examination in all women being evaluated for preterm labor, regardless of the initial index of suspicion. There is no charge for discarded specimens.

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The ACOG bulletin also states that, in order for the fFN test to be "clinically useful, the results must be available from a laboratory within a time frame that allows for clinical decision-making (ideally within 24 hours)."[2] The introduction of a rapid fFN test and its approval by the FDA in September 1998 have greatly improved the utility of determining fFN levels in cervicovaginal secretions. The test itself takes 26 minutes to complete, and most laboratories can get a result back to the clinician within 1 to 2 hours.

OBG MANAGEMENT: What findings on cervical ultrasonography are reassuring for you, and which are nonreassuring?

NORWITZ: The most important measurement on cervical ultrasonography is residual cervical length. Both transvaginal and transperineal sonography are reliable and reproducible ways to assess the length of the cervix,[2,36] although transvaginal sonography is considered by most practitioners to be the gold standard. Mean cervical length changes with gestational age,[30-32] but a cervical length of 2.5 cm or less at 22 to 24 weeks in a pregnancy at high risk for PTD should be considered abnormal and requires further evaluation.

Funneling (or beaking) at the internal os also is concerning as it may indicate an intrinsically weak cervicoisthmic junction suggestive of cervical incompetence, but the data are less consistent. Some studies have found the presence of funneling to be an independent risk factor for preterm birth (independent of cervical length),[37,38] whereas other studies have been unable to confirm this observation.[30,39] It also has been suggested that a "cervical stress test" be performed by applying transfundal pressure and watching for funneling at the internal os, and several studies have shown that a positive test is predictive of PTD.[40,41] Whether such testing should be performed in all women at risk of preterm birth remains unclear.

There are several factors to consider when assessing cervical length and dilatation. These include the orientation of the transducer, the potential distortion of the cervix by the transducer, and the fact that a full bladder may artificially lengthen the cervix and obscure dilatation of the internal os.[42] Careful attention to maternal position also is essential.[43]

All cervical abnormalities should be reported to the patient. Deciding whether to repeat the cervical ultrasound in 1 to 2 weeks versus placing a cervical cerclage versus bed rest should be individualized, and will depend on such factors as gestational age, *a priori* risk of PTD, and patient preference. I typically review in detail the risks and potential benefits of each management option with the patient, and will recommend cervical cerclage if the pregnancy is at high risk of PTD, if the gestational age is less than 24 weeks, and if there is evidence of progressive cervical shortening with a residual length (with or without funneling) of less than 2 cm.

Although I have chosen 2 cm as a cutoff for recommending cervical cerclage, the optimal cutoff value remains controversial, ranging from 1.5 to 3 cm.[38] Whether the cutoff value should differ for women with multiple gestations or women who have had prior cervical surgery is unclear.

Whether cervical length and fFN are additive in their ability to predict preterm delivery in women at high risk remains controversial.

OBG MANAGEMENT: When you use ultrasonography in combination with fFN screening, how do you make decisions based on the combination of results? How do you proceed in the face of discordant findings?

NORWITZ: In my practice, it is unusual for women to be screened with both cervical ultrasound and fFN testing. I use cervical ultrasound more often in the mid- to late second trimester in asymptomatic women with a history of preterm birth suggestive of cervical incompetence, and fFN more often in symptomatic women presenting to the outpatient clinic or L&D unit remote from

term. However, there are a few exceptions. These include women with higher-order multiple gestations (triplets and up), in whom the risk of preterm birth remote from term is extremely high, and symptomatic women at 22 to 28 weeks, when the bimanual examination suggests cause for concern and ultrasound confirms substantial cervical shortening.

Whether cervical length and fFN are additive in their ability to predict PTD in women at high risk, or whether they are simply 2 separate methods of assessing the same pathophysiologic process, remains controversial. Recent data suggest that these tests are indeed additive. High-risk women at 22 to 24 weeks with a residual cervical length of less than 2.5 cm and a positive fFN screening test have a 65% risk of delivering at less than 35 weeks, even if they are asymptomatic at presentation.[2,44]

A negative fFN test excludes imminent delivery, with less than 1% of such women delivering within 14 days of presentation.

Which of the 2 tests is more reliable in any given patient also is not clear. This becomes important when the testing is discordant. In a woman with an abnormal cervical examination remote from term, a negative fFN test is reassuring because the data suggest that she is highly unlikely to deliver within the next 2 weeks.[2] How to interpret a positive fFN test in an asymptomatic woman with normal cervical length, however, is not clear. As the bulletin states: "The clinical implications of a positive test have not been evaluated fully."[2]

My approach to such patients is to increase antenatal surveillance, but not to modify their care in any other way on the basis of a single positive fFN, i.e., no corticosteroids, no tocolysis, no bed rest. I typically will not repeat the fFN test, although some practitioners would recommend repeating it in 1 to 2 weeks if the patient remains undelivered. Although a subsequent negative fFN test cannot "remove" the implications of the previous positive test, some evidence suggests that 2

negative test results following a positive test reduce the risk of spontaneous preterm birth back to baseline.[45]

OBG MANAGEMENT: The bulletin stated that fFN may be useful in "avoiding unnecessary intervention" in symptomatic women by virtue of its negative predictive value. What has been your experience in this regard?

NORWITZ: The first question to ask is how best to define a "symptomatic" woman. ACOG says the following symptoms and signs suggestive of preterm labor deserve further evaluation:

- Uterine contractions (with or without pain)
- Intermittent lower abdominal pain, dull backache, pelvic pressure
- Vaginal bleeding during the second or third trimester
- Menstrual-like intestinal cramping (with or without diarrhea)
- Change in vaginal discharge (amount, color, consistency)
- Vague sense of discomfort characterized as "not feeling right"

This question pertains specifically to symptomatic women presenting to the outpatient clinic or to the L&D unit. Of all women at 24-0/7 to 34-6/7 weeks with symptoms or signs suggestive of preterm labor, about 80% will be fFN-negative, i.e., fFN <50 ng/mL in cervicovaginal secretions. A negative fFN test effectively excludes imminent delivery, with less than 1% (1 in 125) of such women delivering within 14 days of presentation.

A positive fFN test, on the other hand, will predict delivery within the next 14 days in only 16% (1 in 6) of symptomatic women. As such, the value of the fFN test lies primarily in its negative predictive value (124 of 125 women with a negative fFN test will not deliver within the next 14 days).[33-35,45] Indeed, a negative fFN test in symptomatic women has been shown to reduce admissions for preterm labor, length of stay, and use of tocolytic agents,[46] as well as to reduce unnecessary transfers to a tertiary care center.[47] These benefits translate into substantial cost savings[46,47] and likely minimize adverse events in pregnant women by avoiding unnecessary interventions.

OBG MANAGEMENT: What is your screening modality of choice for symptomatic women and why?

NORWITZ: Two key elements should be considered when evaluating a woman who presents with 1 or more symptoms or signs suggestive of preterm labor: the gestational age and the best estimate of the patient's *a priori* risk of PTD. The latter requires knowledge about the presence or absence of risk factors for preterm birth (especially a history of prior PTD), uterine contractility, cervical examination (including dilatation, effacement, and station), presence or absence of ruptured membranes, and fetal well-being.

If the index of suspicion for PTD is high in a symptomatic woman, admit her for observation to exclude preterm labor.

If the index of suspicion for preterm delivery remote from term is high, the patient should be admitted for observation to exclude preterm labor. Antenatal corticosteroid and tocolytic therapy should be initiated, if indicated. Broad-spectrum antibiotic therapy has not been found to be useful in the setting of preterm labor with intact membranes, although there is a considerable body of evidence demonstrating its efficacy in the setting of ruptured membranes at less than 34 weeks.[48,49] Tocolysis has not been shown to be effective once the fetal membranes are ruptured, and is best avoided in this setting.[50]

If there is no evidence of preterm labor and the index of suspicion for PTD is low, the patient may be discharged home, even if she is symptomatic. Careful follow-up should be arranged within 1 to 2 weeks, and the patient should be counseled to return to the office if the symptoms of preterm labor worsen. In this setting—and depending on the gestational age—it may

be appropriate to screen the patient with either fFN or sonographic estimation of cervical length. ■

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