OBG MANAGEMENT

CASE-BASED LEARNING

Predicting and preventing preterm birth

Preterm delivery seems likely, and the nearest tertiary care nursery is 90 minutes away. What should you do?

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PATRICIA'S CASE

A 25-year-old primigravida with an intrauterine pregnancy at 26 weeks presents with contractions of moderate intensity every 4 minutes, intact membranes, and minimal vaginal bleeding. On digital exam, her cervix is soft, 50% effaced, and closed. Estimated fetal weight is 775 g.

You are at a Level I hospital in a rural community, 90 minutes from a tertiary nursery. What steps should you take first?

Tocolytics and antibiotics are the first steps. They may help to maximize the benefits of secondary strategies such as antenatal corticosteroids during transport to a tertiary care facility. In addition, assessment of fetal fibronectin levels and use of endovaginal ultrasound can supplement clinical judgment and improve prediction of outcomes. Their excellent negative predictive value can spare many women unnecessary and potentially harmful treatments.

This article discusses these measures in the context of an actual case.

The value of "secondary prevention"

Giving corticosteroids to enhance fetal lung and brain maturity and transporting the mother to a tertiary care center may not prevent preterm delivery, but they can mitigate some of the damage and are supported by the evidence.

Corticosteroids. Given the clear evidence of their efficacy, steroids should be administered once preterm birth appears likely. I would give steroids before maternal transport.

Betamethasone is preferable to dexamethasone, which may be toxic to the fetal central nervous system. However, dexamethasone is preferable to no therapy.

Contraindications to corticosteroids include systemic maternal or fetal infections and maternal endocrinopathies such as Cushing's disease or poorly controlled diabetes.

Transport to tertiary care. A neonatal intensive care unit clearly benefits tiny babies. Clinicians should be aware of the pediatric capacity of their community hospitals and maintain a referral relationship with the nearest tertiary care centers. Conversely, clinicians on the receiving end of maternal transports should make every effort to expedite these referrals.

IS LOCAL CARE TOO RISKY?

Patricia and her family strongly prefer that she undergo treatment in her own community, if at all possible.

Signs and symptoms of preterm labor are poor predictors of preterm birth. Although most symptomatic women deliver at term, even the most clinically astute physician cannot predict when a symptomatic patient will deliver.

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INTEGRATING EVIDENCE AND EXPERIENCE

Which tocolytic is most effective?

Berkman ND, Thorp JM Jr, Lohr KN, et al. Tocolytic treatment for the management of preterm labor: a review of the evidence. Am J Obstet Gynecol. 2003;188:1648–1659.

No single drug is best. In this metaanalysis, magnesium, β-mimetics, calcium channel blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs) performed about the same at prolonging the interval between onset of preterm labor and actual birth, compared with placebo or no treatment. Ethanol was less effective and "inappropriate." Tocolytics are given to stop contractions (first-line therapy) and to maintain quiescence after an acute episode (maintenance therapy).

To determine the most effective tocolytic, we analyzed 16 studies of first-line therapy and 8 involving maintenance therapy, using the above 5 drug classes.

How 5 drugs compare

Estimated odds ratios suggest that, when used as first-line therapy, all the drugs except ethanol are about the same. Odds ratios ranged from 1.622 for β-mimetics to 2.485 for calcium channel blockers. (The odds ratio for NSAIDs was based on only 1 study.)

When we tested whether β-mimetics, calcium channel blockers, and magnesium sulfate had the same effects, compared with placebo, the results suggested that they do not. However, the body of literature was not large enough to establish this conclusively.

Overall, β-mimetics appear to lack superiority over the other drugs as first-line therapy and cause more maternal harms, while ethanol is "inappropriate" and no longer in use.

As maintenance therapy, none of the drugs appeared to have any benefit.

Maternal and fetal harms

We defined harms as "clinical markers and events that the authors of individual studies considered as adverse events or side effects."

Among maternal harms were serious cardiac side effects, including arrhythmias, heart failure, and chest pain, linked to β-mimetics. Minor cardiovascular harms were also higher among women given β-mimetics. In addition, calcium channel blockers appeared to increase the risk of minor cardiovascular harms, but not as much as the β-mimetics.

Overall, maternal cardiac, metabolic, and psychologic harms were more prevalent among women taking β-mimetics. This may be due, at least in part, to the fact that studies of β-mimetics tended to look for these effects more than other studies did.

As for short-term fetal harms, we found "little consistent evidence" of them in the infants of women receiving these drugs, and the studies lacked sufficient data to evaluate potential long-term harms.

What later analyses found

After 1999, the cutoff year of our review, several relatively large studies showed the oxytocin antagonist atosiban to be effective as acute[7,8] and maintenance[8] therapy, with a favorable side effect profile. Another trial[9] compared 2 doses of magnesium (2 and 5 g per hour); the higher dose acted more quickly but with more side effects. These and other studies do not alter our conclusions about the effectiveness of tocolytic therapy—or the specifics of the 5 drugs studied.

2 useful markers

In the 1990s, 2 biologic markers were discovered that improve the precision of preterm birth risk assessment:

- fetal fibronectin (fFN) and
- endovaginal sonography (EVUSD).[1]

A glycoprotein produced only during fetal life, fFN is concentrated at the interface of the placenta and uterus. The fFN molecules are in vaginal secretions prior to spontaneous childbirth at both term and preterm.

Use of EVUSD enables measurement of the cervix from the internal to external os. Cervices shorten before spontaneous birth.

These 2 tests, when positive (fFN detected or cervical length <2.5 cm), have moderate positive predictive value (20%–40%) but excellent negative predictive value (95%–99%). Negative predictive value is most useful clinically, as with other biologic tests ObGyns use, such as cervical cytology, mammography, and maternal serum screening.

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How corticosteroids protect the fetal brain and lungs

5-1/2 months' gestation

Brain
Sensory nerve cells are developing, increasing in size, and establishing more complex connections as the brain enters a period of rapid growth that will continue until about 5 years of age.

At this gestational age, the fetus still lacks the fissures and sulci that characterize the adult brain.

Besides speeding development, corticosteroids may reduce hypoxic-ischemic injury.

Lungs
The fetal lungs are beginning to develop bronchia, alveoli, and blood vessels, and will soon begin excreting surfactant.

Corticosteroids speed this process.

IMAGE: MAURA FLYNN

FAST TRACK

fFN and EVUSD separately and independently contribute to the prediction of preterm birth. I use both

I use a negative test to identify women who do not require further treatment or evaluation. If a patient has a negative fFN or EVUSD, I would not transport her to a tertiary care center. In fact, I would probably discharge her home with close follow-up.

3 concerns about the tests

Clinicians tend to have some concerns about incorporating these tests into their routines:

- **How reliable is negative predictive value?** Arguably, these tests perform better than clinical judgment and can spare many women unnecessary treatments.[2] No test is perfect, however. These biomarkers should be adjuncts to—not replacements for—clinical wisdom.
- **What about false results?** With fFN, a proper collection kit with plastic tube and Dacron swab is critical because the molecule will adhere to glass or cotton, creating a false-negative result. A false-positive result can occur after recent coitus or a digital cervical exam; therefore, collect fFN specimens before checking the cervix. With EVUSD, the examinations require a moderate amount of skill.
- **Which biomarker is best?** Both fFN and EVUSD make independent and separate contributions to the prediction of preterm birth. Therefore, I use both.

START TOCOLYSIS AND ANTIBIOTICS?

Patricia's fFN and EVUSD tests are both positive. Should you start tocolysis and antibiotic therapy prior to transfer?

Metaanalysis suggests tocolysis, and antibiotics extend the interval between symptom onset and delivery.[1] The length of this prolongation can be measured in days, and no evidence suggests that prolonged pharmacotherapy has any benefit.

I would initiate both therapies while waiting for the mother to be moved to a tertiary center, even though neither therapy has been shown to improve perinatal outcome.

Tocolysis. We could find no differences among tocolytic drugs.[3] Serious side effects are rare, but nuisance cardiovascular symptoms are frequent. Sympathomimetic drugs lead to lethargy, and magnesium is associated with malaise. Magnesium requires intravenous access and should be given only via infusion pump by trained personnel. That often means a nurse must accompany the patient to the Level III hospital.

Thus, for logistical reasons, I favor nonsteroidal anti-inflammatory drugs, of which indomethacin is the most widely studied. Indomethacin can be given by mouth or rectum, with minimal side effects. Harm to the fetus is rare if the drug is used acutely for only 48 to 72 hours (the maximum duration of any potential benefit).

Antibiotics. Current protocols calling for betalactam antibiotic therapy as prophylaxis against early-onset neonatal sepsis in preterm births have led to almost universal use of antibiotics among these patients. Our metaanalysis did not demonstrate superior pregnancy prolongation with any other regimen, so the one for group B strep prophylaxis provides a double benefit.[4] As with tocolytics, there is no role for maintenance therapy.

WHEN CONTRACTIONS CEASE

Patricia is transferred and completes her steroid therapy. Her symptoms and contractions cease. After a few days of observation and no cervical changes, she is discharged home. She asks about home therapies, work, activities, and sex.

Since our metaanalysis of tocolysis studies showed no efficacy for maintenance regimens, I do not recommend them except in this rare situation: when a woman has so much uterine activity without cervical change that she is unable to rest or complete her daily activities. In this case I would favor "as needed" doses of a β-mimetic drug by mouth.

Although home uterine activity monitors and subcutaneous tocolytic pumps are available, evidence suggests they are ineffective.[1] I seldom, if ever, use these devices.

Despite the almost universal recommendation that women at risk of preterm birth avoid physical and sexual activity, we lack evidence that bed rest or abstinence prolong pregnancy or prevent preterm birth.

Is sex allowed? When we studied both physical activity and sexuality in asymptomatic women at midpregnancy, neither was associated with spontaneous preterm birth.[5,6] Therefore, I do not recommend restricting activity or sexual intercourse. Instead, I encourage women to carefully assess uterine activity. If certain behaviors appear to increase contractions, those behaviors should be limited.

Counsel her to trust her instincts. It is important to encourage the patient to trust her own instincts, so that an overzealous employer or partner cannot coerce or cajole her to do something that violates her internal sense of well-being. ■

FAST TRACK

I favor indomethacin. It is the most widely studied NSAID and has minimal side effects

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