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PRACTICAL STRATEGIES

Prevention of recurrent preterm birth

A ROUNDTABLE DISCUSSION

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Dr Al-Khan has nothing to disclose. Dr Hwang reports that he is a member of the speakers' bureau for Adeza Biomedical. Dr Rebarber reports that he has received grants/research support from and is a consultant to Adeza Biomedical and that he is a member of the speakers' bureau of Adeza Biomedical and Matria Healthcare. Dr Roman reports that she is a consult to and member of the speakers' bureau for Adeza Biomedical. Dr Stettler reports that he is a stock/shareholder and member of the speakers' bureau for Adeza Biomedical.

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Since 1981, the incidence of preterm birth—defined as delivery at 20 to 37 weeks gestation—has increased from approximately 9.4% to the current rate of 12.7%;[1] which itself is an increase over the previous year's rate of 12.5%.[2] The annual cost of preterm birth is estimated at more than $26 billion. Of premature infants who survive, 10% to 15% have significant handicaps (See "Morbidities associated with preterm birth").[3] Although the risk of morbidity and mortality is much higher for very premature infants, clinicians need to be aware of the risks associated with late preterm birth. Birth between 35 and 36 weeks has 3 times the risk for mortality compared with normal length of gestation.[4] The most significant risk factor for preterm birth is a prior preterm delivery, although African American race also increases risk, as do vaginal bleeding and bacterial vaginosis.[5] Clearly, any preterm birth should be regarded as an important risk factor for subsequent preterm birth.

This roundtable discussion reviews the issues faced by obstetricians and perinatologists in the management of patients at risk for recurrent preterm birth and describes available treatment options that may improve outcomes.

DR REBARBER: Overall, what is your view on the current increasing rates of prematurity? How serious is the problem we face?

DR AL-KHAN: Clearly preterm labor and delivery has become an epidemic in developed countries.This problem is compounded by the fact that current treatment options are known to be ineffective.

Aggressive management is crucial in terms of identifying those patients at high risk for preterm delivery and offering early intervention. While 17 alpha-hydroxyprogesterone caproate (17P) is only indicated at present for use in women who have had previous preterm deliveries, it may have utility for those patients with other risk factors for preterm labor, eg, higher-order multiples and perhaps short cervix.

Aggressive and preventative treatment protocols are commonly used by other specialties. For instance, cardiologists treat patients at risk for myocardial infarction using strategies encompassing behavior modification and pharmacologic agents. In addition, in the setting of an acute ischemic event, aggressive intervention has resulted in improved outcomes. Perhaps we should apply a similar logic to the treatment of prematurity. Prematurity represents a common obstetrical disorder, yet years have passed by and we have not been successful in meeting this challenge.

DR HWANG: The most important service we offer our patients is a reduction in complications related to prematurity. Unfortunately, we often see these patients late in the pregnancy, when we have few options. A very thorough evaluation of the obstetrical history is critical to help us understand events in the prior pregnancy that may have contributed to prematurity. New treatment options include the administration of 17P and the use of fetal fibronectin tests. These improve our ability to diagnose and prevent recurrent preterm birth.

Morbidities associated with preterm birth

- Anemia
- Apnea
- Cerebral palsy
- Infections resulting from immature immune system
- Intraventricular hemorrhage
- Jaundice
- Mental retardation and learning disabilities
- Necrotizing enterocolitis
- Neonatal death
- Periventricular leukomalacia
- Respiratory distress syndrome
- Retinopathy

DR REBARBER: Certainly, information that clarifies occurrences in prior pregnancies is extremely helpful in order to counsel patients on recurrence rates. While prematurity is a clear event, its causes are complex. Research has not elucidated the biochemical pathways that lead to this outcome. It might be more appropriate to define preterm birth as a syndrome, not as one disease and entity. The process includes decidual hemorrhage, infection, inflammation, maternal and/or fetal stress, or uterine overdistention.

DR ROMAN: I agree that it is critical to arrest the process that initiates preterm birth prior to onset of preterm labor or membrane rupture. Of the preterm births in the United States, about 70% are spontaneous. The risk for recurrence ranges between 21%[6] and 45.1%.[7] Risk increases with the number of preterm births and how early in gestation the birth occurs. Patients with recurrent preterm birth represent a very high-risk population. The most powerful weapon in our arsenal is 17P.

DR STETTLER: I agree that preterm birth is becoming an epidemic, and as an obstetrician/gynecologist and perinatologist, I am deeply concerned. As noted, prematurity is associated with increased perinatal mortality and potential for life-long handicaps.

Management of at-risk patients is not a simple task. The causes of preterm birth are a heterogeneous group. Treatment, therefore, involves much more than just starting these patients on medication once a risk factor is identified. Management must begin prior to conception with optimum nutrition and maternal health. Proper diet, smoking cessation, and effective management of chronic maternal disease all have roles in the prevention of recurrent preterm birth.

I have found that most women with a history of preterm birth will be much more "involved" during subsequent pregnancies. This is particularly true if they were counseled at the time of their initial preterm delivery regarding the need for improved health and informed of its pregnancy-related benefits. Simply put, starting a pregnancy in the best possible health is a great benefit.

DR HWANG: We must also assess substance abuse and evaluate the patient's socioeconomic factors, as these are associated with prematurity.

We have good evidence that maternal and fetal stress can activate the hypothalamic-pituitary-adrenal axis. Basic science data suggest that adrenal hormones, cortisol, prostaglandin H synthase 2, and prostaglandin E2 are harmful in patients at risk for preterm labor. It's important to assess their stress factors and stress level, in terms of psychological, physical, and emotional stress. Patients may need psychological evaluation. Strategies to reduce the stress levels are helpful. Issues that are unrelated to the pregnancy but that are causing stress should be identified.

DR STETTLER: Once they are pregnant, women at risk for recurrent preterm birth need an aggressive plan of surveillance and management. The use of cervical ultrasound and fetal fibronectin will aid in identifying women at risk of preterm delivery in a current pregnancy.[8] 17P has been shown to reduce recurrent preterm delivery in a select group of women with a history of previous preterm birth as a result of spontaneous preterm labor or preterm premature rupture of the membranes.[7]

Sadly, no evidence supports the use of interventions such as tocolytics, bed rest, or cerclage as prophylaxis against recurrent preterm birth. Therefore, I would not treat an at-risk patient without labor with tocolytics; this would require unnecessary treatment in a large number of patients and subject them to potential side effects. To illustrate, the Meis study[7] showed a recurrent preterm birth rate of 45.1% in the control group. If I treated all of the at-risk patients (based on the Meis inclusion criteria) with tocolytics starting early in pregnancy, I would unnecessarily expose 55% of the women to these medications. Conversely, good evidence from the same randomized controlled trial suggests that administration of 17P is beneficial. Therefore, I would prescribe this for patients that fit the Meis inclusion criteria, as supported by the American College of Obstetricians and Gynecologists (ACOG).

DR HWANG: It is disappointing that many studies have failed to show efficacy of our interventions, but this may be because clinicians often use every intervention available to help patients maintain pregnancies; placebo-controlled trials are seldom practical.

Objective measures for surveillance

DR REBARBER: How do you use objective measures of risk for prematurity, such as cervical length and/or fetal fibronectin results, to identify high-risk patients?

DR ROMAN: We take cervical length measurements at 2 to 3 week intervals from about 16 to 28 weeks of pregnancy. We use fetal fibronectin between 22 and 32 weeks of pregnancy at 2- to 3-week intervals.

DR HWANG: Once we identify at-risk patients, we increase surveillance by using fetal fibronectin and serial transvaginal cervical length assessments. The literature indicates that this is the best combination.

DR STETTLER: I would like to point out that March of Dimes data suggest that recurrent preterm birth accounts for about 10% of the total preterm births annually. While our discussions center on prevention of recurrent preterm birth, we also need to develop effective monitoring strategies for patients without histories of preterm birth.

For patients at risk for recurrent preterm birth, I use both fetal fibronectin and cervical length assessment as objective assessments of pregnancy progress rather than as risk assessment tools. We already know they are at risk. I begin serial cervical length assessments in the second trimester, usually between 16 and 20 weeks gestation. For patients with a history of very early preterm birth, I start at 16 weeks. Very early preterm birth may have a component of incompetent cervix; identification of this patient may allow cerclage placement. In someone with a history of delivery at 22 to 24 weeks, it is often difficult to determine if cervical dilatation occurred prior to labor or vice versa. I then use fetal fibronectin evaluation at 24 to 28 weeks in addition to cervical length assessment.

This approach is supported in the literature. The Preterm Prediction Study[9] showed that a positive fetal fibronectin result at 22 to 24 weeks predicted 63% of the preterm births prior to 28 weeks, a period when there is very significant associated morbidity and mortality. The study also revealed that, within the group of women with a history of preterm birth, use of cervical length with fetal fibronectin allowed identification of pregnancies that were at high risk of recurrence versus those at low risk. Iams et al also documented this predictive ability.[10]

Assessment of cervical length is a very safe procedure. How we interpret it may lead to problems. For this reason, it cannot be relied upon as a stand-alone test. History, current pregnancy history, physical exam, and fetal fibronectin are all additional pieces of information that can help us to better care for our patients.

DR REBARBER: How would you manage a patient who shows a shortened cervical length, a positive fetal fibronectin result, and a history of preterm birth?

DR AL-KHAN: In the patient with a shortened cervix and a positive fetal fibronectin result we attempt to identify the possible etiology of the positive test. For example, does she have an infection, such as cervicitis or bacterial vaginosis? Is there subchorionic bleeding or abruption? Is semen present?

I agree with Dr Hwang that a thorough history is critical. Because this patient is definitely at risk, I would start 17P therapy. If she has any evidence of contractions or dynamic cervical change, I would then consider administration of a calcium-channel blocker. Early intervention is essential.

DR STETTLER: In this particular scenario, I would start the patient on 17P at 16 to 20 weeks gestation per the Meis protocol. When I note a short cervix and a positive fetal fibronectin result, I obtain a detailed interval history. I need know about any recent changes, such as any increase in pelvic pressure, low back pain, menstrual type cramping, bleeding, or increased vaginal discharge. I would monitor for contractions and do an ultrasound to evaluate for subchorionic bleeding, as suggested by Dr Al-Khan. I would assess for vaginitis and urinary tract infection. The results of this evaluation determine treatment.

This woman would certainly need to restrict activity. I recommend that any such patient maintain good nutrition and hydration, and contact me for any changes she perceives. I would begin to see this patient for follow up at least weekly. If there is evidence of labor, I would start tocolytic therapy. If there is no evidence of labor, then a decision regarding cerclage needs to be made. This determination is rarely clear cut, but involves evaluation of previous pregnancy history, current gestational age, and current physical findings. Of note, short cervical length and positive fetal fibronectin can resolve, as evidenced by the Preterm Prediction Study.[8]

Administering antenatal steroids

DR REBARBER: Would you administer antenatal steroids in the setting of a short cervix and positive fetal fibronectin test?

DR STETTLER: I would administer steroids if the patient were at or beyond 24 weeks' gestation and I felt preterm delivery was imminent, as would be the case if there were evidence of preterm labor.

DR ROMAN: We, too, give steroids to reduce the neonatal morbidity and mortality if the patient is at or beyond 24 weeks' gestation. We use 17P according to the

17P: Structure, history, and a review of the literature

The active ingredient of 17P is 17 alpha-hydroxyprogesterone caproate (HCP). The naturally occurring substance has significant progestational activity and duration of action. It is not converted to androgens, estrogens, or corticosteroids.

The sterile injectable solution contains 250 mg/mL 17-HPC, castor oil, benzyl benzoate, and benzyl alcohol. 17P is currently available only from compounding pharmacies. It is identical to a previously marketed product, Delalutin, introduced in 1956[1-3] and used in the prevention of recurrent miscarriage and risk of miscarriage, among other indications.

A recently completed multicenter randomized placebo-controlled trial conducted between 1999 and 2002 enrolled 463 patients with a documented history of previous singleton preterm delivery. At randomization, the fetuses had gestational ages of between 16 and 21 weeks. Excluded patients had a history of multifetal gestation, known major fetal abnormality, prior progesterone or heparin treatment during pregnancy, history of thromboembolic disease, or history of maternal medical/obstetrical complications. Participants received weekly IM injections from enrollment until 36 weeks or birth, whichever occurred first. Administration of 17P reduced the rate of recurrent preterm birth at earlier than 37 weeks (32% reduction), earlier than 35 weeks (31% reduction), and earlier than 32 weeks (39% reduction). The percentage of infants born weighing less than 2500 g was reduced, as was the admission rate of infants to neonatal intensive care units. Results were consistent irrespective of the mother's race, number of previous preterm births, or the gestational age of previous preterm birth. The study was halted after interim analysis of 351 patients demonstrated substantial benefit of 17P in reducing preterm birth, and continuation of placebo arm was considered unethical.

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Meis protocol. Several studies of 17P are underway in women carrying multiple gestations and women with a short cervix. We are eagerly awaiting the results of those trials.

DR REBARBER: In my clinical practice I recommend the use of 17P as strictly defined by inclusion criteria in the paper published by Meis et al.[7] Studies from the 1980s evaluated the administration of 17P started at 28 weeks in twins as a prophylactic measure to prevent preterm birth. 17P did not show significant efficacy.[11] I, too, am interested in the outcomes of current trials.

DR STETTLER: We need to keep in mind that 17P is a prophylactic therapy for the prevention of preterm birth, not a treatment for preterm labor. Starting administration of this agent after the onset of preterm labor would not be beneficial. This likely explains why the twin studies, starting 17P at 28 weeks, showed no benefit.

DR HWANG: Several small studies have demonstrated the efficacy of progesterone in the form of vaginal suppositories. It is difficult to make head-to-head comparisons among agents. DaFonseca[12] had a broad inclusion criteria. The primary endpoint was preterm birth. Other outcomes included frequency of episodes of uterine contraction or preterm labor, as well as response to treatment with betamimetics. The incidence of preterm birth was lower in the progesterone arm (13.8%) than in the placebo arm (28.5%). When delivery before 34 weeks was assessed, the rates were 2.8% in the progesterone group versus 18.6% in the placebo group. Mean frequency of contraction was also lower in the progesterone group (23.8%) compared with that of the placebo group (54.3%).

I do use the 17P protocol whenever possible. A large, well designed randomized controlled trial has shown improvement in the outcomes for a high-risk population with the administration of 17P. Why deviate from that?

DR REBARBER: I agree, but we need to put the 17P data into perspective. There are an estimated 48,000 recurrent preterm births in the United States each year. With the use of 17P, we may expect to see a 35% reduction in this number. It may reduce the overall rate of preterm birth by 1% or 2%. The use of 17P may not have a broad scope of impact, given its indication only in patients with a prior spontaneous preterm birth. It is

nonetheless important, as is counseling patients about known risk factors for prematurity and the importance of the preconception consultation to discuss limiting these factors. We also need to better coordinate care with our reproductive endocrinology and infertility (REI) counterparts in order to limit the number of multiple gestations that occur using their various treatment modalities.

DR HWANG: From a clinical practical point of view, I like the patient to make weekly office visits for 17P intramuscular injections. This provides opportunities for additional encounters with our nursing staff. These may reveal important information regarding warning signs and symptoms: Does the patient have cramping? Does she have a urinary tract infection of which she was unaware? In addition, we can evaluate compliance issues regarding 17P and discuss possible adverse events from injections.

Issues of fertility and prematurity

DR REBARBER: What about the potential impact of fertility management on prematurity? Should we counsel patients about multifetal pregnancy reduction prior to treatment courses? Should we consider the single embryo transfer models being used in Europe?

DR STETTLER: We often see multiples following assisted reproductive technology. The monozygotic twinning rate is higher in in vitro fertilization (IVF) pregnancies than in unassisted pregnancies. Although the problem of increased multiples would not be eliminated by single embryo transfer, it would be reduced. As we all know, multiple gestation constitutes a very high risk situation for preterm birth.

Fortunately, I work very closely with my REI colleagues. As a result, I provide counseling to many of these patients prior to pregnancy. I offer multifetal pregnancy reduction when triplets or higher order multiples are conceived. I also outline a very detailed management plan for these patients, including serial assessment of cervical length and fetal fibronectin testing, as previously discussed.

My center is currently involved in research to evaluate the use of 17P in twin and triplet pregnancies for the reduction of preterm birth. I offer participation in this randomized controlled trial to all twin or triplet pregnancies that meet criteria. However, I do not give 17P to multiple gestations outside of this research protocol.

DR AL-KHAN: We treat a large patient population referred by our REI colleagues. Clearly, there is strong evidence of an increased incidence of preterm labor and delivery with IVF, even in the presence of singletons. Data from Goldsmith and Weiss[13] suggests the possible role of relaxin in this process. This could be occurring as early as the first trimester.

For women pregnant with triplets and higher-order multiples, I offer reductions. I also give the patient the option to continue progesterone therapy beyond the first trimester. While we are waiting for additional data concerning progesterone, we need to remember that the use of progestins dates to the 1940s, hence its safety is not questioned.

We also need to remember that these patients often have reached a high level of stress and anxiety while trying to conceive. Stress has clearly been associated with preterm labor and delivery.

DR ROMAN: We have found that fetal fibronectin retains its negative predictive value in patients who have undergone multifetal pregnancy reduction. It is an accurate test in that situation and also when cervical cerclage is used.[14,15]

Omega-3 fatty acids and preterm birth

DR REBARBER: Dr Roman, can you suggest other strategies that may prevent preterm birth, particularly in light of your recently published work?[16]

DR ROMAN: Published data suggest that omega-3 fatty acid supplementation is helpful in preventing recurrent preterm birth in women with a prior spontaneous preterm birth. Recurrent spontaneous preterm birth was reduced from 33% to 21% and a difference in mean birth weights between the groups was reported.[17]

We supplement high-risk patients with omega-3 fatty acids derived from algae, available in several products. We also use prenatal vitamins that contain docosahexaenoic acid (DHA). The Danish trial[17] used fish oil, 2.7 g per day, which is significantly higher than the dosing currently available in prenatal vitamins. But that total included only 900 mg of DHA. Commercially available tablets each contain about 200 mg of DHA. I tell my patients to take a prenatal vitamin with DHA in it and an additional omega-3 fatty acid supplement.

What is the place for tocolytics?

DR REBARBER: We have all alluded to the use of tocolytics. Can we discuss this in more detail? If there is a failure with the use of nifedipine, for example, would you use the terbutaline pump? Retrospective and observational studies have evaluated the terbutaline pump; and the data are conflicting. As Dr Al-Khan noted, a major problem is how to interpret the data. In most studies, preterm birth has been looked upon as a single outcome.

Use of 17P: ACOG recommendations

- Treatment should be dictated by clinical circumstances and physician preference; tocolytic agents show no clear efficacy in perinatal outcome as maintenance or repeated administration.
- The use of antibiotics should be limited to group B streptococci prophylaxis.
- Use of 17P is recommended to prevent recurrent preterm birth.
- Tocolytic drugs have shown efficacy in short-term pregnancy prolongation of 2 to 7 days, which may allow clinicians to administer steroids to accelerate fetal lung maturity and transport the mother to a more appropriate care facility.
- Cervical ultrasound examination and fetal fibronectin tests are useful to predict patients at risk for preterm delivery. Either approach or combined use of these modalities may help to identify patients who do not need tocolysis. Amniocentesis may be useful to assess fetal lung maturity and intra-amniotic infection.
- Such traditional interventions as bed rest, hydration, and pelvic rest do not show efficacy in reducing the rate of preterm birth.

ACOG Committee Opinion. *Obstet Gynecol.* 2003;102:1115-1116.

No pathophysiologic pathways were identified to define which patients were best suited for the various treatment strategies. Measures to prolong gestation were initiated late in the process, in relation to cervical change and activation of chemical pathways toward prematurity. Does anyone think there is a role for the terbutaline pump in patients that we may identify earlier? The data in the daFonseca trial showed that betamimetic therapy may be sensitized by progesterone.[12]

DR HWANG: It is discouraging to hear such negative reports about tocolytics; I use them on a case-by-case basis. We cover a wide geographic area in our practice and may have a patient traveling a long distance who has a 3-cm cervix and active preterm labor. I would use nifedipine or magnesium to assist with maternal transport to an appropriate facility.

In a short course and acute phase of preterm labor, I use nifedipine as well as similar agents. If I'm putting a cerclage in, I may administer indomethacin for a short course. While a short duration of tocolytics may have some clinical utility, I do not use maintenance tocolytics; the data do not support their use.

DR ROMAN: I agree with Dr Hwang: Based on the evidence, nifedipine appears to be one of the most effective tocolytics available. As shown in a Cochrane review of clinical trials, nifedipine is more effective than magnesium and betamimetics and it has fewer side effects. We are starting to use nifedipine in the acute setting for acute tocolysis in preterm labor patients.[18]

DR AL-KHAN: I limit the use of cerclages to those patients with clear clinical indications. I would rather treat them early with progestins and nifedipine if indicated. The combination of a calcium channel blocker and progesterone early in the game has been effective in my experience. There are no prospective trials to support this management strategy, but I foresee it becoming a common practice.

DR STETTLER: Tocolytics are probably the most used medications in pregnancy, second only to prenatal vitamins and antibiotics. From the responses here, everyone on the panel, including myself, uses them. Although it is beyond the scope of this discussion to delve into the details of tocolytics, it will suffice to say that none of the current agents used for tocolysis are truly successful. As for the Cochrane Collaboration, I think that many have extended the data beyond what the findings actually showed. As an example, the evaluation of nifedipine for preterm labor only showed that nifedipine "is as good as and possibly better than ritodrine." The Cochrane reports did not make the same statement regarding magnesium; only a single comparative study was included. However, 2 randomized controlled trials comparing calcium channel blockers to magnesium demonstrated equal efficacy.[19,20] Therefore, I do not feel that adequate evidence exists to suggest that nifedipine is a superior tocolytic in terms of efficacy to other agents.

I agree with Dr Rebarber that we need to better define the various pathways of preterm labor. Once this is done, we may then be able to develop truly effective tocolytics. Does this mean that we should not use tocolytics now? Of course not. A delay in delivery of 48 hours will allow time for administration of antenatal corticosteroids or transfer to a facility with a higher level of care if needed. Finally, even though tocolytics may not be effective in the majority of patients, they are successful in some. If we can stop labor in one 24-week pregnancy and delay the delivery to 28 or 30 weeks, the outcome is drastically improved both from a quality-of-life standpoint and degree of financial burden.

DR REBARBER: What if patients fail first-line nifedipine therapy? Would you use maintenance tocolytics to prevent recurrent admissions to the hospital?

DR ROMAN: The data do not support the use of maintenance tocolytics or are conflicting. On a case-by-case basis, we use maintenance tocolytics primarily to keep patients out of the hospital and to reduce visits to the OB triage with complaints of contractions. We found that to be effective. Dr Al-Khan, have you used the terbutaline SQ pump?

DR AL-KHAN: I don't use terbutaline, as its efficacy as maintenance therapy has not been demonstrated in the literature.[21] Furthermore, there are side effects. Nevertheless, use of this agent has been shown to delay delivery for 24 to 48 hours, which may be of benefit in allowing time for corticosteroid therapy or maternal transport to a tertiary care facility.

In the acute setting, we no longer use magnesium sulfate and we encourage our generalists to discontinue its use as a tocolytic agent. We advocate the use of indomethacin for the first 36 to 48 hours and synergistically add a calcium-channel blocker until 34 to 35 weeks of gestation. In addition we administer progesterone 48 hours later in select patients. This regimen is well tolerated with fewer adverse effects.

DR REBARBER: Nifedipine is favored by the panel. We agree that magnesium is the least popular and is the least evidence-based tocolytic. A recent commentary by Grimes notes that the use of magnesium is not supported by the medical evidence and in fact can produce potential harmful effects.[22] Clearly, magnesium tocolysis should be discontinued. Calcium channel blockers are the preferred mode of primary tocolysis, given the current literature.

DR STETTLER: I would not say that I favor nifedipine above all else. The data do not show that it is better than magnesium. The Grimes editorial is clearly food for thought. Unfortunately, Dr Grimes fails to quote more recent literature that rebuffs the alleged increase in perinatal mortality as a result of magnesium exposure suggested by the Cochrane Collaborative.[23] I suspect that strong opinions will soon be published regarding Dr Grimes' commentary; I believe it would be inappropriate to discontinue use of magnesium based on this editorial. In my opinion, after review of the available literature, we do not have any evidence that suggests that one tocolytic (eg, magnesium, ritodrine, terbutaline, nifedipine, nonsteroidal anti-inflammatory drugs) is clearly more efficacious than the rest.

DR HWANG: You raise an important point. As clinicians, we all experience a conflict between what we see throughout our careers and what we read in the literature. We want our efforts to be as evidence-based as possible, incorporating results of research studies. However, the data do not always fit within our own clinical situations. I believe epidemiology and evidence-based medicine are important components of our armamentarium. But there is still a place for our expert opinion and our judgement. We need to talk to our patients and individualize the treatment options. I feel there are roles for cerclages and tocolytics in certain situations.

DR ROMAN: I agree: Individualizing care is the most important principal.

DR REBARBER: Very true. The pathways to prematurity are not well understood, and therefore our data conflict. Prematurity represents one final event, and we have developed varying interventions based on that event. Therefore, it is difficult to determine what is efficacious for the individual patient since there are differences in the etiologies leading to that common pathway.

Antibiotics: Increases in preterm risk?

DR ROMAN: What intuitively makes sense often isn't borne out in the literature. As an example, trials have evaluated the use of antibiotics to prevent preterm birth in at-risk patients (based on risk factors and positive fetal fibronectin). Two trials found that fetal fibronectin positive patients treated with antibiotics delivered earlier than the patients who were not treated with antibiotics. Not only was antibiotic therapy not helpful, it appeared to be somewhat harmful in those patients. This underscores how little we know about what causes preterm birth.[24,25]

Even in terms of agents that we know are effective, we have theories but incomplete data about the mechanisms of action. This is true of progesterone and omega-3 fatty acids. Until we have this understanding, agents should be used with caution.

DR HWANG: We used to give antibiotics, such as amoxicillin and erythromycin, to patients who showed any threat of preterm labor. I was very impressed with Oracle I and II trials examining neonatal outcomes in over 7,000 patients given antibiotics. Ampicillin and its analogs were associated with higher rates of neonatal death, chronic lung disease, or major cerebral abnormality.[26] As a result, I have changed my practice; I don't administer ampicillin even in the presence of ruptured membranes. Instead, I rely on the macrolides, the only medications that have been shown to improve neonatal outcomes. I will administer azithromycin or a similar agent, as tolerated by the patient. Our patients can only benefit if we narrow down the population that we serve, use cervical length and fetal fibronectin to assess risk, and then apply interventions that we know are effective.

DR STETTLER: Clearly, we must individualize our therapies to the patient, but we also must use our research as

a guide. Indeed, antibiotics have not been shown to reduce preterm birth. However, in those patients with preterm labor, I still administer penicillin (or alternative therapy) for group B streptococci (GBS) prophylaxis unless I have a negative culture. I also use azithromycin in patients with preterm premature rupture of membranes, in addition to penicillin or ampicillin for GBS prophylaxis.

Can we provide too much surveillance?

DR ROMAN: There does not appear to be fetal harm associated with administration of 17P. It's been studied in tens of thousands of pregnancies with no evidence of any adverse affects.

DR AL-KHAN: I absolutely agree with the rest of the group. One has to be very careful in caring for high-risk patients. Often we, and our patients, reach a point of desperation. We want to do everything possible to improve the outcomes for our patients and their newborns.

I think we ought to be cautious with cervical length monitoring and its incorporation into clinical practice. More and more cervical length measurements are being performed in today's practice. This has led to more morbid and probably unnecessary procedures and interventions, such as cerclage placement, yet the incidence of prematurity is still rising.

We cause more harm by performing unnecessary and/or unindicated tests. We introduce morbidity by placing an unnecessary stitch that can potentially become infected. Remember, the vagina is not a sterile organ; the moment we place a stitch or administer antibiotics, we alter the vaginal flora and hence add more insult.

DR HWANG: We evaluate the patient and the benefit to her of cervical length assessment. In my opinion, this surveillance often decreases the amount of surveillance required for the majority of patients who have normal cervical length. I believe we need to restrict the use of cervical assessment to those who have risk factors.

DR REBARBER: I agree; the cervical length measurement has been very popular, but we need to limit its use to clinically relevant situations and understand who should get screened. A study by the Nicolaides group assessed cervical length in a low-risk population in the midtrimester. Shortened cervical measurement led to cerclage intervention in a prospective randomized fashion and did not improve outcomes.[27]

In visualizing the cervical length, clinicians need to determine if the patient is functionally normal but shortened or abnormal and if inflammation is present. Fetal fibronectin, rather than cervical length measurement, may be helpful in answering such questions. Other tests that may be useful in the future must provide information about the biochemical pathways that lead to prematurity.

Practical application: A case study

DR HWANG: How would you treat a nulliparous woman at 22 weeks' gestation who presents with a deep cervical funneling, cervical length of 0.5 cm, and no symptoms?

DR AL-KHAN: Clinically, in a patient who has a short cervix, I look for the presence of funneling and its degree. If a significant width is funneled (you need to be certain that the sonographer is obtaining accurate images since improper probe placement can make a cervix appear shorter or longer) and the patient has risk factors, I would then offer cerclage placement. Otherwise, I don't believe cerclage is effective. Additionally, the criteria for cervical insufficiency have become more lax; we no longer go by the classic criteria of 3 recurrent losses. No one wants to wait to lose 3 babies before you put in a stitch. Patients, and their doctors, want to put it in after 1 loss or perhaps with just a short or funneled cervix. So we must be very careful while assessing our patients. I would watch the patient if she has no risk factors and postpone intervention. Recent investigations bear this out.[28,29]

DR REBARBER: What if she decides on cerclage?

DR AL-KHAN: I would be reluctant to put a stitch in the patient. I think it adds to the morbidity. Let me give you an example: I had a patient who came from an outside institution. She was 22 weeks primigravida with a short cervix and funneling. A stitch had been placed. Two days later she ruptured her membranes, became septic, and went into septic shock.

DR STETTLER: This case is an example of one of the most difficult situations we face. There is no previous pregnancy history to help us. If she is not having contractions and is without evidence of infection, then the possibility of incompetent cervix must be raised. I agree with Dr Al-Khan in that we must be sure that our cervical images were appropriately obtained.

Yet, I would disagree that a patient should suffer any losses prior to recommending cerclage, especially in cases such as this. Once a deep funnel is present, we know the internal os is incompetent. In this patient, the residual cervical length is only 0.5 cm, which is highly abnormal.[30] She should be evaluated for evidence of labor by uterine tocodynamometry even though she has

no symptoms. If there is no evidence of labor, I would recommend cerclage. Furthermore, if the cervix were dilated, then I would first do amniocentesis to evaluate for intra-amniotic infection. If negative, I would proceed with cerclage if the patient agreed. Now, I do offer the patient the option of expectant management. However, if cervical dilatation occurs during this time, then outcome is detrimentally effected, even if a cerclage can be placed. Once the cervix opens, the risk of bacterial contamination of the chorion-decidual layer (which we have no way to directly evaluate) and the intra-amniotic space increase. This then elevates the risks of preterm labor or preterm premature rupture of membranes, as may have been the case in Dr Al-Khan's example.

DR ROMAN: I agree that it is a difficult decision. A key step in patient evaluations is contraction monitoring: if a woman is contracting, that lends to a diagnosis of preterm labor as opposed to cervical incompetence. We would not place the stitch in this patient unless she developed cervical dilatation. We would perform an amniocentesis to evaluate for intra-amniotic infection. If she did develop cervical dilatation, we would first test for infection. If the results were negative, we would consider cerclage.

DR AL-KHAN: This is an important point, but it can be difficult to accurately diagnose infection. For example, a negative amniocentesis does not rule out early intra-amniotic infection or infection at the level of the choridecidua.

DR REBARBER: Romero and colleagues noted that perhaps the presence of interleukin (IL)-6 and IL-8 are more sensitive markers of infection.[31]

DR STETTLER: I agree. Once these tests are available routinely in all settings, I think they will greatly add to our ability to prevent very serious infections, as in the example presented by Dr Al-Khan.

Bed rest: A useful intervention?

DR ROMAN: What about bed rest? It is so controversial. There are not a lot of data. Do you use bed rest?

DR HWANG: I do put patients on bed rest. I believe this can reduce maternal stress factors and activation of cytokines. We see a lot of prematurity in a lower socioeconomic patient populations. These women might have several jobs and stressful lives. I believe that helping a patient take a week off work is a reasonable option. Studies by Crowther[32] and Goldenberg[33,34] did not show evidence that bed rest improves outcomes. What about in-hospital observation? That is controversial, as well.

DR AL-KHAN: I think bed rest could help, but strict bed rest can add morbidity for some patients. Strict bed rest in patients who are already hypercoagulable increases the risk of deep vein thrombosis (DVT) and perhaps pulmonary embolism. That being said, we know that preterm labor and delivery are not gravity-induced; the mechanisms are complex.

DR STETTLER: I hate to tell patients they need to be at bed rest. It is impossible outside of the hospital, potential morbidities are associated with bed rest, and bed rest has never been shown to decrease preterm birth.

DR REBARBER: I don't think that bed rest helps in the overwhelming majority of cases; we have yet to define a population in which it is effective. It poses inherent risks. Patients may benefit from a modified level of activity and decrease in workload, perhaps by decreasing the maternal stress response. In patients who have cerclages, concerns regarding ascending infections and prostaglandin release in semen has led me to recommend pelvic rest.

DR ROMAN: We don't use strict bed rest: There is a 1% to 2% risk of DVT with bed rest, not taking into account the potential impact of comorbidities such as obesity. I agree that it may be helpful to limit activity for some patients. Strict bed rest almost always requires that the patient be hospitalized with strong consideration given to the risk of DVT and appropriate prophylaxis, whether through the use of compression devices or low-dose heparin.[35]

DR REBARBER: I would emphasize a modified activity level in a patient over 22 weeks and perform a fetal fibronectin test at more than 24 weeks. Depending on risk factors, I would administer antenatal steroids to accelerate lung maturation. We would monitor for contractions and perhaps use nifedipine if we notice that there are more than 4 to 6 contractions in an hour, sustained for 2 hours. We would use some interventions but accept some of the limitations as to their utility. Proper patient counseling is paramount at this time.

Arresting the inflammatory process?

DR ROMAN: We haven't discussed indomethacin. While this agent needs more study, it may help arrest inflammatory processes that contribute to a short cervix. It may therefore represent a promising treatment early in gestation.[36]

I limit indomethacin to 48 hours of use in most cases and follow the patient closely for fetal effects, such as oligohydramnios and premature closure of the ductus arteriosus. We establish a baseline by amniotic fluid index. After 48

hours, we make a decision whether to continue. If we decide to continue treatment, we follow the pregnancy with twice weekly assessments of amniotic fluid volume. Additionally we perform a baseline fetal echocardiogram and follow up with weekly echoes to make sure that the ductus arterious remains open.

We do not use indomethacin after 32 weeks of gestation and we try to wean patients from this agent at 28 weeks of gestation.

DR REBARBER: I believe we are largely in agreement regarding our treatment protocols. Prematurity represents a complex syndrome and we are trying to map out the pathways biologically. We are also trying to treat at much earlier endpoints and better define the pathways for individual patients. Unfortunately, most, if not all, of the available therapies do not distinguish among potential causes of prematurity. Therefore, it is difficult to select therapies that best meet the needs of individual patients; this limits our interpretation of the various treatment trials available.

DR HWANG: I believe we all face similar challenges in incorporating the evidence into our practice while individualizing treatment for our patients.

DR ROMAN: I agree, and it is exciting to have new agents such as 17P, as well as dietary supplements.

DR AL-KHAN: This is an evolving field. Let's hope new research will clarify our treatment protocols. Large prospective randomized controlled clinical trials will ultimately help us separate effective from ineffective therapies.

DR STETTLER: We are slowly gaining more knowledge in the area of preterm birth. The information on 17P concerning its ability to reduce recurrent preterm birth is very beneficial. However, the challenge of decreasing preterm birth in those patients without a history remains. As this group accounts for 90% of preterm births, we need to direct our efforts along this path. ■

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