Prevention of Preterm Birth: A Pivotal Role of Progestogens

ANNOUNCER INTRODUCTION

Welcome to CME on ReachMD and the Omnia Education activity, Prevention of Preterm Birth: A Pivotal Role of Progestogens.

Your host is Dr. Parithma Setty. Dr. Setty will speak with Dr. Andrew Combs is the Associate Director at the Research at Obstetrix Collaborative Research Network in San Jose, CA.

Dr. Combs has nothing to disclose.

This CME activity is supported by an independent educational grant from Lumara Health.
After listening to this activity, participants should be able to:

- Describe the risk factors for the pathogenesis of Preterm Birth (PTB), as well as the economic burden/cost of illness
- Discuss the available efficacy and safety data for the current progestogen agents, and the relevance of those data for FDA approval
- Demonstrate understanding of the ACOG/SMFM redefinition of “term pregnancy”
- Incorporate strategies for providing optimal clinical management to women at risk for PTB, based on SMFM and ACOG recommendations
- Define the differences in quality standards between “pharmacy-compounded” 17P and those of the FDA-approved product

Dr. Setty:

Pre-term birth, which is before 37 weeks gestation, presents the most important challenge in today’s obstetrics. With over 26,000 infant deaths each year the United States ranks 55th in the world for infant mortality. Nearly 70% of babies who die before their first birthday were born prematurely. Twelve percent of pregnancies in the United States occur pre-term and are associated with significant infant mortality and morbidity. Pre-term birth is extremely expensive and accounts for 50% of all pregnancy costs. The Institute of Medicine examined the cost of pre-term birth and estimated the economic toll in 2005 to be 26.2 billion, or 51,500 per infant born pre-term. As clinicians, what are we doing to address these issues? What are the latest recommendations for screening and treatment? And most importantly, how do we impact our patients’ lives?

I am your host, Dr. Prathima Setty, and I am joined by Dr. Andrew Combs, who will answer these questions and much more. Dr. Combs, welcome to CME on ReachMD.

Dr. Combs:

Thank you and it’s a pleasure to be here this morning.
Dr. Setty:

ACOG recently defined the concept of term pregnancy. What does it mean to achieve a term pregnancy?

Dr. Combs:

Well, ACOG, in a recent committee opinion, actually subdivided the broad category of term pregnancy into various subcategories. So term pregnancy has traditionally meant any gestational age between 37 weeks up to 41 weeks and 6 days. And with their new definition, what ACOG did, was subdivide this into: Early-term, which is from 37 weeks and 0 days to 38 weeks and 6 days; full-term which is from 39 and 0 days to 40 and 6 days; and late-term which is from 41 weeks of gestation to 41 weeks and 6 days. Pre-term is still defined as anything before 37 weeks of gestation and post-term defined as anything after 42 weeks of gestation. But by subdividing term pregnancy, what ACOG hoped to do, was put emphasis on the idea that we really ought to be avoiding births before 39 weeks of gestation, not just 37 weeks of gestation. Children born at 37 to 38 and 6 are still at increased risk for respiratory morbidity and other complications, and do have a higher rate of mortality and serious morbidity, compared to babies born at 39 weeks and beyond.

Dr. Setty:

What role does pre-term birth play in neonatal morbidity and mortality in the United States?

Dr. Combs:

Well Dr. Setty, as you mentioned previously, 70% of infant mortality, that is death before the age of 1, occurs in births that are pre-term. So clearly, neonatal mortality and infant mortality are largely driven by pre-term birth in the United States and serious morbidity as well. Pre-term delivery is the number one risk factor for morbidity and mortality of normal infants. There is still some morbidity and mortality associated with anomalous fetuses. So abnormal babies do have a higher risk of morbidity and mortality, but this has fallen to a number two cause.

Dr. Setty:
So you mentioned some of the risk factors. What are the other common risk factors for pre-term birth?

Dr. Combs:

Well there are a large number of risk factors and these vary in their prevalence and their importance. A very important risk factor is a history of a pre-term birth in a prior pregnancy, which confers about a 3-fold increased risk. A history of hypertension carries a risk of pre-term birth, due to preeclampsia or fetal growth restriction. A history of smoking carries a risk of spontaneous pre-term birth both related to fetal growth restriction as well as pre-term labor. African Americans have approximately twice the risk of pre-term birth compared to Caucasians. History of bleeding in the first trimester carries about a 1.5-fold increased risk of pre-term birth. So there is a variety of risk factors. The problem is that when we look at those that are born pre-term, the majority actually is identifiable risk factors that would have been discovered based on routine history or examination screening.

Dr. Setty:

Dr. Combs, what is the economic burden of pre-term birth on the healthcare system and specifically, on our Medicaid system, in the United States?

Dr. Combs:

Well Dr. Setty, you had mentioned earlier that the Institute of Medicine estimated the cost of pre-term births in 2005 to be about 26 billion dollars to the United States. Some of that is direct medical cost related to care of the baby initially after birth, but there are also indirect costs such as need for special education which accounted for 1 to 2 billion. There is increased cost in terms of care of the mother which amounted to another 1 to 2 billion. And then, there is about 6 to 8 billion dollars estimated cost of loss of productivity, because children that are born pre-term are at higher risk for having neurodevelopmental problems and may not be as productive in the workforce. In terms of financial impact and economic burden on the Medicaid system and federally-funded healthcare, it is important to realize that Medicaid, nationwide, provided coverage for about 48% of births in the United States in 2010. And for several states that figure was well over 60%. This rate has been increasing on the average and in light of the Affordable Care Act and Medicaid Expansion; the rates are expected to rise even further. Additionally, Medicaid pays about twice as much for any adverse outcome compared to private insurers. For most Medicaid payors, NICU admissions constitute the most expensive...
hospitalization, so clearly quality improvement initiatives to prevent pre-term births can bring significant savings to Medicaid (inaudible)*6:40 by both increasing equitable access to screening modalities, identifying patients at risk, as well as utilizing therapeutic approaches demonstrated to be effective at reducing the risk of pre-term birth.

Dr. Setty:

If you are just tuning in, you are listening to CME on ReachMD. I am your host, Dr. Prathima Setty, and today I am speaking with Dr. Andrew Combs about pre-term birth.

Dr. Combs, what screening and treatment strategies are recommended by SMFM and ACOG to reduce recurrent pre-term birth in women with a history of prior pre-term birth?

Dr. Combs:

Well the recommendations that you’re asking about come in two separate documents that were published independently by the two organizations but, by and large, are in agreement on the major points. The Society of Maternal Fetal Medicine published a paper in the American Journal of Obstetrics and Gynecology, which they called A Clinical Practice Guideline, Progesterone in Pre-term Birth Prevention. This appeared in May 2012. The American College of OB/GYN, or ACOG, published a practice bulletin in October of 2012 on The Prediction and Prevention of Pre-Term Birth. Both documents were in agreement that for women with a history of a prior pre-term birth, that preventive therapy with 17- hydroxyprogesterone caproate, which I will refer to from now on because that’s mouthful, as 17-OHPC. Preventive treatment with this medication starting at about 16 to 20 weeks of gestation and continuing to 36 weeks of gestation, will reduce the recurrence risk of pre-term birth in women with a history of prior pre-term birth. So both organizations recommend giving this treatment prophylactically to women with a singleton pregnancy and a history of a prior spontaneous pre-term birth.

The documents differ slightly on the role of cervical length screening. We know that about 40% of women who ultimately go on to deliver pre-term, can be identified in the late second trimester by the basis of having a short cervical length on transvaginal ultrasound screening. The SMFM document
recommends serial transvaginal ultrasound screening be done in women with a history of prior pre-term birth, starting at about 16 weeks of gestation, and continuing to 23 weeks and 6 days. The recommendation is to do this every 2 weeks. The ACOG practice bulletin on the other hand, was a little bit vague as to whether or not they actually recommend this. They reviewed the data, identifying a short cervix, and treating women with a short cervix by giving them a cerclage, has been proven to be beneficial. But the document itself is silent on whether and how often a screening of cervical length should be done.

Dr. Setty:
What about screening and treatment strategies recommended by SMFM and ACOG to reduce pre-term birth in women with no history of prior pre-term birth?

Dr. Combs:
Here the documents are actually in agreement. Both recognize that identification of a short cervix might identify a population of women with no prior history as being at high risk of pre-term birth. Both documents reviewed the evidence that treatment with vaginal progesterone is beneficial in this setting at substantially reducing the risk of pre-term birth if the cervix is short. So both documents say that it is reasonable for patients with no history of prior pre-term birth to have a screening examination of cervical length done at roughly 20 weeks of gestation. However, both documents recognize that not every OB/GYN practice has the capability of performing cervical length screening; that not every ultrasound practice has providers who are certified to provide accurate cervical length screening, etc. And in light of the practical considerations, what both documents conclude is that it is reasonable for providers to offer cervical length screening if they know how to do it, and are properly trained and certified, but they do not make it mandatory.

Dr. Setty:
Can you summarize the differences between vaginal progesterone and 17-alpha hydroxyprogesterone caproate injections as to their efficacy, safety, and FDA indications?

Dr. Combs:
Yes. So of the two, only 17-hydroxyprogesterone caproate, 17-OHPC, is FDA approved for the prevention of pre-term birth and this approval was given for women with a history of a prior spontaneous pre-term birth, and a singleton pregnancy in the current pregnancy. This FDA approval was granted on the basis of a large clinical trial that showed a roughly 33% reduction in pre-term birth overall, and an almost 50% reduction in early pre-term births in women given this treatment when they have such as history.

The FDA did not approve vaginal progesterone for this indication. In fact, no company has applied to the FDA for such an approval. And one company applied for an approval for vaginal progesterone for treatment of a short cervix. But the FDA did not grant the approval for treatment in a short cervix because there was only one trial supporting efficacy and the efficacy was not strong enough to support it based on a single trial. And, at this point, no other company has applied for approval, to my knowledge, for vaginal progesterone for treatment of a short cervix. So at this point, if we use vaginal progesterone, which is available as an FDA-approved medication for other indications, so we give it off label. So we have FDA-approved medications, but not specifically labeled for the indication of pre-term birth prevention. We can give it for treatment in a short cervix.

Dr. Setty:

Is there a role for progestagen therapy in other patients at high risk for pre-term birth such as those carrying twins?

Dr. Combs:

Well the data on twins are somewhat controversial. Both the ACOG bulletin and the SMFM bulletin apply only to women who have singletons in the current pregnancy. And the reason for this is that there is not substantial evidence saying that progestagen therapy is useful in preventing pre-term births in twins or triplets. There are 8 randomized trials evaluating the role of progestagens in preventing pre-term birth in women with twin pregnancies, without other risk factors, and all of these showed negative results. And meta-analyses have concluded that there is no evidence suggesting that either 17-hydroxyprogesterone caproate or vaginal progesterone is useful in preventing pre-term birth in twins overall. However, subgroup analyses, suggest that vaginal progesterone is as effective in women with twins with a short cervix, as it is in women with a singleton pregnancy and short cervix. So many
practitioners will give vaginal progesterone in the setting of a twin pregnancy with a short cervix, although this is not currently endorsed by either ACOG or SMFM, because there is no single trial that *bullet 14:41* points to efficacy in that setting.

Dr. Setty:

17-OHPC is currently available through the brand, Makena, and through compounding pharmacies as well. When prescribing 17-OHPC, what are the advantages of prescribing an FDA-approved product over a compounded product?

Dr. Combs:

Well FDA-approved products, in general, whether they’re brand name or whether they’re generic, are controlled in their manufacturing process by a set of principles called, Good Manufacturing Processes. And the FDA reviews the actual step-by-step manufacturing process; inspects the facilities where the manufacturing is done; requires that the manufacturer actually tests the product to be sure that it has the right chemicals, the right potency, that it’s pure, that it’s sterile, that it doesn’t have contaminants in it, etc. Whereas, compounded medications are basically homemade. A compounding pharmacy will obtain the raw materials from suppliers and will mix the chemicals together in their own facility. And although accredited compounders will follow a set of principles dictated by the US Pharmacopeia, there’s actually generally no testing of the product to be sure that it’s pure, that it’s potent, that it doesn’t contain contaminants, that it’s sterile, etc. And the lack of testing is sometimes a cause for concern. Many of you may remember the debacle that happened a couple of years ago, when the New England Compounding Center, was sending out vials of contaminated methylprednisolone which caused hundreds of cases of fungal meningitis and over 50 deaths. This is a problem with compounded medications is that there’s no testing for sterility. And although this was an isolated incident, one never knows when the next such incident might happen.

Dr. Setty:

Dr. Combs, where do you see ACOG and SMFM going in regards to pre-term birth in the future?

Dr. Combs:
I think we’re seeing an era where there’s increasing cooperation between various professional organizations in circling the wagons around the area of pre-term birth prevention. Last August of 2014, the Society of Maternal and Fetal Medicine, the American College of Obstetricians and Gynecologists, and the American College of Nurse Midwives, collaborated in sending a letter to the Secretary of the Department of Health and Human Services, Sylvia Mathews Burwell. In this letter, they outlined the economic and social impact of pre-term birth, some of the problems, and some of the consequences, and some of the risk factors. And they outlined some strategies for collaborating to prevent pre-term birth. And specifically, they talk about in singleton pregnancies with a history of prior spontaneous preterm birth, their recommendation for broader availability of the use of 17-OHPC; some breaking down of some of the barriers to the availability of this medication which is sometimes denied by payors, and especially public payors, because it’s somewhat expensive. But in terms of the cost savings at the end, there is clearly a case to improve utilization. There’s also a recommendation for use of vaginal progesterone in patients who have short cervical length and the cost effectiveness of doing this. This is actually a very cheap medication. They estimate that the cost of the course throughout the entire pregnancy is under $400 and compared to the cost of a pre-term birth, which is estimated at over $50,000 on the average—clearly a huge cost savings.

And then, they talk about some of the possibilities of where things could go with collaboration between the organizations; I think creates support from Health and Human Services to make these therapies more broadly available. Universal transvaginal cervical length screen with followup with treatment of short cervix is estimated to reduce pre-term birth less than 33 weeks by 45%; a 50% reduction in births before 28 weeks of gestation; 61% reduction in respiratory distress syndrome; 25% reduction in NICU admissions. So I think we’re seeing an era of increased cooperation between a variety of professional organizations, and hopefully some movement on the part of the Federal government, who have clearly a vested interest in preventing pre-term births, because they’re the primary payor for all the expenses of pre-term births.

Dr. Setty:

Well I want to thank very much our faculty, Dr. Andrew Combs, for joining us today.

Dr. Combs:
Thank you very much for the opportunity to participate. I hope that the listeners gained some useful information from this.

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