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Antibiotic Therapy and Preterm Labor

ABSTRACT & COMMENTARY

THORP AND ASSOCIATES REVIEWED 107 ARTICLES DEALING WITH the use of antibiotics to lengthen pregnancy in patients with preterm labor (PTL). After applying stringent inclusion criteria, Thorp et al eventually extracted data from 14 randomized clinical trials (RCTs), which evaluated antibiotics vs. placebo or no treatment. They evaluated 3 end points: length of prolongation of pregnancy; gestational age at birth; and birth weight.

One study showed improvement in all 3 outcomes. Five studies indicated no improvement in any of the variables. Four found significant prolongation of pregnancy and 2 found a decrease in the proportion of preterm deliveries.

The RCT meta-analysis revealed modest benefits from antibiotics: significant pregnancy lengthening by 6 days, a significant increase in gestational age at delivery by only 4 days, and a nonsignificant increase in birth weight by 70 g. (Thorp JM Jr, et al. *Am J Obstet Gynecol*. 2002;186:587-592.)

COMMENT BY JOHN C. HOBBINS, MD

The obvious rationale for the use of antibiotics in PTL is that infection is the culprit behind many preterm deliveries. However, since PTL can result from a myriad of causes, it is difficult from the available literature to tell what percentage of patients in PTL would truly benefit from antibacterial therapy. There is no uniformity of opinion among researchers with regard to antibiotics in PTL. However, 2 vocal factions have emerged: the totally committed and the naysayers. Fortunately, many investigators still seem to be on the fence while waiting for more data to surface before deciding whether antibiotics for all PTLs make sense.

Based on the available data, one cannot dismiss an infectious etiology for at least some PTLs. The prevailing current theory is that bacteria take an extra membranous pathway upward from the cervix, alighting in a location where they set up an active area of infection. Here, phospholipase A is liberated from interaction with the decidua. This, in turn, results in the release of arachidonic acid from the

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INSIDE

membranes, which is the precursor of the prostaglandins causing contractions.

Theoretically, all this can happen without the bacteria seeding the amniotic cavity, an event that occurs later in this scenario. In a series of publications spanning 10 years, Roberto Romero and his various team members demonstrated that between 9.2% and 12.8% of patients admitted with PTL and intact membranes had a positive amniotic fluid culture, and that 32% of patients who delivered within 48 hours had a positive culture. The group then went on to show that a cytokine, interleukin-6, was the most sensitive amniotic fluid indicator of intra-amniotic infection, followed by WBC count, glucose, and Gram stain. Later, in the same clinical setting, the group showed that elevations of various cytokines were more indicative of histologic evidence of chorioamnionitis than a positive amniotic fluid culture, suggesting that an infectious process, not yet of intra-amniotic proportions, can be responsible for PTL and delivery.

If we were to theorize that only 20-30% of PTLs are related to infection, then one would have to treat 3-4 patients with antibiotics for the one that could possibly benefit from the treatment. This could have some bearing on the modest benefit demonstrated in the above meta-analysis. Also, it is clear that most patients randomized into the above studies are not in true PTL, and therefore, the effect of any treatment would be diluted appreciably. Last, in 11 of the 14 studies in the meta-analysis, ampicillin was used, which may not be the right antibiotic to do the job.

For these reasons, certainly the concept of antibacterial therapy may not have been given a fair chance to succeed, especially if there had been a better noninvasive way to identify those patients who had an early infection.

That said—now a word of caution. There is now a strong suspicion that cerebral palsy (CP) may be more related to intrauterine infection than fetal hypoxia. The Romero team has shown in the rabbit that white matter lesions similar to periventricular leukomalacia (PVL), a precursor of CP, can be produced by introducing *Escherichia coli* into the intrauterine cavity. In a separate study, they found various inflammatory cytokine activity in the brains with 15 of 17 neonates with PVL, compared with only 3 of 17 matched control specimens without PVL. Last, in another study, cord blood cytokines were demonstrated to be significantly elevated in infants born preterm with evidence of PVL, compared with preterms without the finding by the third day of life. In fact, IL-6 elevations were noted in 74% of infants with PVL, and this finding stood alone when multivariate analysis weeded out other variables such as chorioamnionitis. This latter result implies that the cytokines might be the cause of PVL, rather than simply being the innocent harbinger of intra-uterine infection.

This investigation suggests that some fetuses would benefit more from being in a nursery than from being continuously exposed in utero to bacteria/cytokines, and that attempts to prolong pregnancy through tocolytics and possibly ineffective antibiotics may not be a good idea.

Frankly, it is difficult to be dogmatic about whether patients with preterm contractions empirically should be given antibiotics. Certainly, it is more important to determine through cervical length and/or fetal fibronectin whether a patient is really in PTL before undertaking any type of antilabor therapy. ■

Suggested Reading

1. Romero R, et al. *Am J Obstet Gynecol*. 1991;165: 821-830.
2. Romero R, et al. *Am J Obstet Gynecol*. 1992;166:

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1382-1388.
3. Romeo R, et al. *Am J Obstet Gynecol*. 1993;169: 805-816.
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Estrogen Replacement on High-Density Lipoprotein Cholesterol in Women with Coronary Disease

ABSTRACT & COMMENTARY

Synopsis: *Of the 10 estrogen-receptor polymorphisms, one was associated with increased estrogen action as evidenced by a doubling of the expected HDL increase during estrogen replacement with conjugated equine estrogens.*

Source: Herrington DM, et al. *N Engl J Med*. 2002; 346:967-974.

In this study, Herrington and colleagues asked whether sequence variants in the gene encoding estrogen receptor alpha modified the effect of hormone replacement therapy (HRT) on levels of high-density lipoprotein cholesterol in postmenopausal women. The women were participants in the Estrogen Replacement and Atherosclerosis (ERA) trial. A total of 309 unrelated postmenopausal women with established coronary artery disease (CAD) were randomly assigned to receive 0.625 mg of oral conjugated equine estrogen (CEE) per day, CEE plus 2.5 mg medroxyprogesterone acetate per day, or placebo. Participants were followed an average of 3.2 years for progression of angiographically defined CAD. Plasma samples were collected annually after an overnight fast. There were 8 known polymorphisms of estrogen receptor alpha and 2 more were discovered. Increases in HDL cholesterol following either HRT arm were greatest in women who were homozygous for the less common alleles in intron 1, particularly the IVS (intervening sequence)1-401 polymorphism. There was insufficient power to determine if this increase in HDL afforded a better clinical result, ie, fewer coronary events or regression of CAD on angiography. However, the increase in HDL in that group was more than twice the increase observed in other women. Based on previous data, the observed increase would be expected to lower the risk of coronary events by 26-39%. Further, in 2 small clinical trials, the effects of estrogen on bone mineral density were greatest in women with the IVS1-401 polymorphism, indicating greater estrogen action. One mechanism may be that the polymorphism allows for a transcription factor known as myb. If so, this may increase estrogen action by altering transcription rates or the stability of mRNA transcripts.

COMMENT BY SARAH L. BERGA, MD

I realize that this is a complicated paper. It introduces a concept that most people would rather not know about, which is that not all women are the same at the molecular level. This field is generically referred to as "pharmacogenetics," meaning that if 2 people have the same circulating concentration of a drug, they will not necessarily have the same response to the same drug level because of differences in their molecular machinery. If not all estrogens are the same and not all women respond equivalently to a given estrogen, doesn't that make it exceedingly difficult to know what to do when prescribing HRT? And isn't the prescribing physician on a collision course with managed care companies who limit the time the physician has to spend with patients, the testing that can be done, and the types of estrogens that the patient is entitled to use? Further, if the circulating concentration doesn't provide sufficient guidance, how are we to tell if the estrogen so given is achieving the desired effect? In essence, we must resort to the bioassay, ie, we will have to assess surrogate outcome measures for medical events and make sure that there is change in the appropriate direction. But to do that well, we must have relatively reliable surrogate markers for important clinical conditions likely to beset the patient. Staying well is getting ever so much more complicated!

While pharmacogenetics is complicated, it does introduce another layer of potential rationality into the world of prescribing HRT. However, the potential is presently more latent rather than actual. What should we do in the meantime? First, we need to try to define as best we can the conditions that the patient might be at risk for developing as she ages. Some of these are generic; some are specific to individual patients. Second, we need to fall back on physiological benchmarks. As a general rule in endocrine replacement, one wants to replicate physiology. What usu-

ally hinders the attainment of this goal is the lack of a suitable product or the cost or cumbersomeness of using that product. Fortunately, for ERT, we do have relatively easy-to-use products that closely replicate physiology, ie, transdermal estradiol patches. We know that the ovary, unlike the thyroid or the pineal, produces almost identical amounts of estradiol during an ovulatory menstrual cycle in all women. However, since HRT is not strictly giving hormones for a disease state, it is not clear if we should try to mimic the ovarian levels of a 25 year old or if we should aim for a somewhat lower level, but one that accomplishes the individually derived clinical objectives. At present, I am voting for the latter course. ■

Exercise During Pregnancy: What is the Effect on the Placenta?

ABSTRACT & COMMENTARY

Synopsis: *These data indicate that a high volume of moderate-intensity, weight-bearing exercise in mid and late pregnancy symmetrically reduces fetoplacental growth, whereas a reduction in exercise volume enhances fetoplacental growth with a proportionally greater increase in fat mass than in lean body mass.*

Source: Clapp JF, et al. *Am J Obstet Gynecol.* 2002; 186:142-147.

A RECENT ARTICLE FROM CLAPP AND COLLABORATORS has shed some important light on placental development and its relationship to fetal growth. Clapp et al took 75 healthy, regularly exercising pregnant women and randomized them into 3 weight-bearing exercise regimens that they pursued 5 days a week through pregnancy. The intensity of the exercises was gauged according to the time spent: 20 min (low), 40 min (moderate), and 60 min (high). One group consisted of women doing high-intensity exercise up until the 24th week, then diminishing their exercise to low intensity thereafter. Using the same 24-week division, a low/high group also was randomly created along with a third moderate/moderate group.

Clapp et al found that the low/high group delivered babies that were lighter and had less fat than either the moderate/moderate or high/low group. The most striking difference occurred in the high/low group, in which participants who had babies who were on average 3900 g compared with the low/high group of 3300 g, and had 12% body fat compared with an average of about 8% between the other 2 groups. Also, placental volumes, ultrasonically measured, were consistently larger in the high/low group.

■ COMMENT BY JOHN C. HOBBINS, MD

This comprehensively designed and beautifully implemented study is one of many carried out throughout the years by Clapp and various colleagues. At first glance, one might consider the clinical connotations of the study to be less than earth shaking, since none of the infants was clinically compromised by any of the exercise schedules. Although the low/high babies were lighter and scrawnier than the others, none had a weight below the 10th percentile. However, this should not be surprising since the study group was chosen for its normalcy, and one would expect little pathology to be generated from this healthy, active, pregnant population.

Clapp et al set out to test a hypothesis that evolved from their earlier work, which suggested that high intensity exercise stimulated stem villous development in early pregnancy and discouraged terminal villous development in late pregnancy. Therefore, an optimal exercise regimen would be to exercise early and often up to 20 weeks and to lay off somewhat in the third trimester. The fact that the high/low babies were bigger, fatter, and had larger placentas proved their point.

So what clinically relevant information can we take away from this study? New techniques of placental casting have yielded exciting information regarding placental development. Basically, there are 3 stages of placental development. During the first stage, primitive primary stem villi extend downward from the fetal surface to provide a structural framework for later activity. The second stage occurs during the second trimester when the initial villi will branch into 10-15 immature stem villi. Not surprisingly, this has been entitled the "branching angiogenesis" stage. The third stage involves the budding out of terminal villi from the existing intermediate villi. Transfer of oxygen and nutrient is dependent upon the amount of terminal villi. This stage has been labeled "nonbranching angiogenesis."

Any process that interferes with either or both of these 2 stages can result in compromise of fetal growth and well being. Smoking, altitude, and maternal anemia can affect these phases of placental development. In many cases of IUGR, where almost uniformly fewer terminal villi are found in the placentas studied, a single cause cannot be identified.

I have taken away (with some embellishment) the following messages from this study:

1. In normal, healthy pregnancy exercise is not overtly

dangerous and may even enhance fetal placental growth if undertaken in early pregnancy.

2. If a patient is at risk for IUGR (having delivered a growth-restricted fetus in a previous pregnancy) or has a condition that would not contra-indicate exercise, one might be able to optimize placental development by a regimen of exercise in the first and second trimester of pregnancy.
3. If IUGR is diagnosed in mid-to-late pregnancy, pursuing high intensity exercise is not a good idea (since the fetus can use any extra terminal villi that can be recruited). In fact, we have had many patients diagnosed to have IUGR in the third trimester, with no obvious cause who have responded with increased fetal growth and improved Dopplers by simply limiting maternal activity. Often these are upwardly mobile types with high-pressure jobs requiring high-energy expenditure. If the placenta has a marginal capability to feed a fetus who is becoming more demanding of nutrients, one can optimize placental perfusion by stopping the maternal competition for the blood supply to the fetus. ■

Resource Use for Patients Undergoing Hysterectomy with or without Lymph Node Dissection for Endometrial Cancer

ABSTRACT & COMMENTARY

Synopsis: *Age and racial/ethnic differences in comorbid illness, complications, and resource use exist for patients undergoing hysterectomy for endometrial cancer. Quantification of the complexity of care is of utmost importance for allocation of sufficient resources.*

Source: Brooks SE, et al. *Gynecol Oncol*. 2002;85: 242-249.

Brooks and colleagues conducted a population-based analysis of patients undergoing hysterectomy for endometrial cancer in Maryland from 1994 to 1996. Of 1281 women undergoing hysterectomy, 91% had total abdominal hysterectomy, 6% underwent vaginal hysterectomy, 2.5% underwent radical hysterectomy, and 0.3% underwent laparoscopically assisted vaginal hysterectomy. Lymph node dissection was performed in 32% of the cohort. Neither age, nor race, nor comorbid illness influenced admission to teaching hospitals. Comorbidity was documented in 56% of cases. African Americans were more likely to have one (P = .002) or > 1 comorbid illness (P = .045) than Caucasians. The most common complications were anemia (13.6%), infection/fever (12%), cardiac (9.4%), pneumonia (8%), ileus (5%), and bowel obstruction (5%). These complications occurred with higher frequency in teaching hospitals (P = .0001), in large hospitals (P = .0001), and in African American patients compared to Caucasians (P = .028). Multivariate regression analysis revealed that older age, admission to teaching or large hospitals, lymph node dissection, heart disease, and African American race were associated with significantly higher resource use. Brooks et al concluded that age and racial/ethnic differences in comorbid illness, complications, and resource use exist for patients undergoing hysterectomy for endometrial cancer. The differences in resource use for teaching hospitals may be reflective of the severity of complications, which are indirectly determined by length of stay. Given the higher costs and skills required to care for elderly women with comorbid disease and complications, quantification of the complexity of care is of utmost importance for allocation of sufficient resources for the care of women with endometrial cancer.

■ COMMENT BY DAVID M. GERSHENSON, MD

The study findings reported herein are important, in that they detail that advanced age and ethnicity are associated with differences in comorbid illness, complications, and resource use for women with endometrial cancer undergoing surgery in Maryland. Previous studies have documented that African American women with endometrial cancer have a significantly decreased survival rate compared with Caucasian women. This study drills down to some of the reasons for this disparity—comorbid illnesses and complication rates. Of course, this population-based study did not include those women whose comorbidity precluded surgery; such women might be treated with radiotherapy alone, hormonal therapy, or no treatment at all. As Brooks et al also point out, the African American patients in their study were more likely to be uninsured or insured by Medicaid, suggesting that survival may be linked to income level. It is not surprising that teaching hospitals had higher rates of complications and longer lengths of stay, but the precise reasons for this finding remain elusive. There apparently was no difference in the rate of comorbidity between patients

admitted to teaching hospitals vs. other types of hospitals. One wonders if more advanced disease resulting in more complicated treatment played a role in this observation. This study addresses resource use in a common cancer for women and underscores the need for further study in this area. ■

Special Feature

The Cost Effectiveness of Pap Smear Screening

By Kenneth L. Noller, MD

I AM VERY WORRIED ABOUT THE FUTURE OF CERVICAL cytology screening. The Pap smear is the single best cancer-screening tool ever developed. It has resulted in approximately a 70% reduction in cervical cancer in all countries in which it has been used regularly. It is not perfect. A single smear probably misses almost as much disease as it picks up. However, cervical neoplasia is such a slowly progressing lesion that even if it is missed the first time, it will certainly be discovered if the woman is screened as few as several times a decade. An ever-higher proportion of cases of cervical cancer in the United States are among those few women who are never or rarely screened.

Despite this remarkable record of success, more and more techniques are being developed for the purpose of improving cervical cytology sensitivity. The introduction of the endocervical brush was one of the first advances. Unlike the more recent techniques, the brush was relatively inexpensive. The more recent changes (liquid-based cytology and HPV-DNA testing) will add tremendously to the cost of Pap smear screening if we continue our current practice of screening every women every year.

Why are we so convinced that annual cervical cytology screening is a good idea? Of course the best answer is that it has been demonstrated to work. Nonetheless, there is little evidence in the literature that screening needs to be annual, and a growing body of evidence that less frequent screening is just as effective and more cost efficient. Recently, 2 articles appeared in the *Journal of the American Medical Association* that used advanced modeling techniques to examine the cost effectiveness of various methods of evaluating ASCUS Pap smears and the possible role of HPV-DNA testing in screening.[1,2]

It is often difficult for us clinicians to read cost-effectiveness articles, as the mathematical modeling techniques are quite difficult to understand. Perhaps the best way to approach reading articles such as these is first to identify the underlying hypothesis, then to look at the assumptions made by the authors in the methods section, and finally to read the comments. Often, many of the details in the methods section as well as the results section are meaningless, clinically. Rather, it is the interpretation of the results from the model that is most important. Both of these recent articles have done a good job of developing their model.

One thing should be very obvious to any clinician who reads a cost-efficiency paper: The assumptions made by the authors are always open to criticism. Much like a case-control study where it is always possible to criticize the controls, the assumption made by the authors concerning costs, frequency of abnormalities, etc, may not be in concert with our own practices. Those who carefully read the literature before attempting to apply modeling techniques usually wind up with generally acceptable results. I believe the *JAMA* article that reviewed the various methods of management of ASCUS Pap smears represents such an article. While I can find things in it with which I disagree, overall it is based on excellent clinical information and its results are probably true.

But back to my main point. I am very worried about the future of Pap smear screening if we continue to believe that every woman needs a Pap smear every year. When the test only cost $8 or $10, such an approach was reasonable. Now, when a Pap smear using liquid-based cytology can easily be billed at $50-100 and if HPV testing is indicated an additional $100 added, will third-party payers continue to allow us to screen every year?

I think the answer is surely "No." Rather, third-party payers are going to demand that the whole area of Pap smear screening be examined carefully, and that an entirely new system of screening be developed. This might mean less frequent screening, but with better techniques. It might mean fewer colposcopic examinations for women with minimally atypical smears, and hopefully will result in much less "treatment" of LGSIL lesions in young women. While there is no official position as yet, the American Cancer Society is currently examining the whole area of cervical cytology screening and should be ready to report within the next few months. I would be amazed if we do not see major changes in their new recommendations compared to our general practice of annual screening.

Perhaps it will be easier for all of us to change our practice if we remember that there never was a scientific basis for annual Pap smear screening. Rather, at least in the United States, annual screening developed more as a result of the availability of oral contraceptives in the 1960s when a woman could not obtain a refill for her OC's without a

Pap smear than from data. While yearly cytology reduces cervical cancer, so does biennial or triennial screening as demonstrated in many published trials. ■

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1. Mandelblatt J, et al. *JAMA*. 2000;287(18):2372-2381.
2. Kim JJ, et al. *JAMA*. 2000;287(18):2382-2390.

CME Questions

1. **In the cost-effectiveness evaluation of a clinical technique based on mathematical modeling, the section of a paper that is the most criticized portion is:**
   a. evaluation of the literature.
   b. interpretation of the literature.
   c. mathematical technique utilized.
   d. assumptions made.
   e. interpretation of results.

2. **All of the following factors are true of African American women with endometrial cancer compared with Caucasian women, *except*:**
   a. decreased survival.
   b. more comorbid illness.
   c. greater rate of being uninsured.
   d. higher complication rate.
   e. shorter length of hospital stay.

3. **Which of the following best describes what is known about estrogen-receptor alpha polymorphisms?**
   a. They are unlikely to be of any clinical significance.
   b. They may be of clinical significance, but it is not clear to what degree and in what context.
   c. The exact mechanisms by which the estrogen receptor alpha polymorphism IVS1-401 confers increased estrogen action are known, but the clinical significance is not.
   d. Women with the estrogen receptor polymorphism IVS1-401 have been demonstrated to have fewer coronary events when given estrogen replacement therapy as compared to women with other estrogen receptor polymorphisms.
   e. Herrington reported a strong positive association between the estrogen receptor polymorphism IVS1-401 and accelerated atherogenesis.

Readers are Invited. . .

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