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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Preterm Premature Rupture of Membranes: When to Deliver?

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: A recent large multicenter, randomized clinical trial has shown that delivering patients with premature preterm rupture of membranes at 34 weeks, rather than pursuing a watchful waiting approach until 37 weeks, does not afford greater protection against neonatal sepsis.

SOURCE: Morris JM, Roberts CL, Bowen JR, et al; PPROMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of membranes close to term (PPROMT trial): A randomised controlled trial. *Lancet* 2016;387: 444-452.

Preterm premature rupture of membranes (PPROM), defined as rupture of membranes prior to 37 weeks, is responsible for about one-third of premature deliveries. When rupture of membranes occurs, decision-making regarding the timing of delivery has been based on weighing the risks of prematurity against the risk to the mother and fetus of ascending infection. To help with this, the American College of Obstetrics and Gynecology (ACOG) published recommendations this year which, admittedly, were based on "limited and inconsistent scientific evidence."[1] Basically, the ACOG Practice Bulletin suggested that if patients had attained 34 menstrual weeks before ROM, they should be delivered.

This recommendation generally has been followed by clinicians, but many have remained skeptical about this 34th week cutoff. To revisit this common management approach, results from a large multi-country, randomized, clinical trial (RCT) were published in *Lancet*.[2] The study involved 65 centers in 11 countries. Patients who were between 34 weeks, 0 days and 36 weeks, 6 days with documented rupture of membranes were randomized to have either immediate delivery or expectant management, including those positive for Group B streptococcus.

Nine hundred twenty-four patients had immediate delivery and 915 were managed expectantly up until 37 weeks, or until there were signs of infection or fetal compromise. Neonatal sepsis was essentially the same, with 23 patients (2%) in the immediate group and 29

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patients (3%) in the expectant group (relative risk [RR], 0.8; 95% confidence interval [CI], 0.5-1.3). Composite neonatal morbidity and mortality were similar, with 8% in the immediate group and 7% in the expectant group (RR, 1.2; 95% CI, 0.9-1.6). On the downside, immediate delivery was associated with significantly higher rates of respiratory distress syndrome (RR, 1.6; 95% CI, 1.1-2.3) and need for any type of ventilatory support (RR, 1.4; 95% CI, 1.0-1.8). Also, infants spent more time in the newborn special care unit (4 days vs. 2 days) ($P < 0.0001$). Mothers in the immediate group had a higher cesarean section rate (26% vs. 19%, 95% CI; 1.2-1.7).

There were some checks in the good column for the immediate group. They had lower rates of antepartum and intrapartum hemorrhage (RR, 0.6; 95% CI, 0.4-0.9), intrapartum fever (RR, 0.4; 95% CI, 0.2-0.9), and need for antibiotics (RR, 0.8; 95% CI, 0.7-1.0). Not surprisingly, the expectant management group had longer maternal hospitalizations ($P < 0.0001$), since 75% of these patients were managed in the hospital.

■ COMMENTARY

It has been assumed that once membranes have ruptured, the barrier to bacterial access into the amniotic cavity is removed, exposing the patient to a ticking septic time bomb. However, this study suggests that immediate delivery of patients with PPROM between 34 and 37 weeks does not necessarily prevent neonatal sepsis — the main reason the aggressive approach was adopted. Instead, one is now faced with a significant increase in cesarean section rate, respiratory distress syndrome, and longer stays in the NICU for respiratory support. The cost of longer maternal hospitalization is easily exceeded by the bloated daily costs of supporting babies in the NICU.

So, at least until the next study surfaces, it seems that if avoiding sepsis is our primary goal, watchful waiting in patients with PPROM between 34 and 37 weeks appears to be a viable alternative, and may prove to be even a better one. ■

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ABSTRACT & COMMENTARY

Factor V Leiden Mutation and Combined Hormonal Contraception? Is Thrombosis Risk Acceptable?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: A meta-analysis of cohort studies supports that women with mild thrombophilias like heterozygote Factor V Leiden mutation can use combined hormonal contraception if other reliable methods are not acceptable.

SOURCE: van Vlijmen EF, Wiewel-Verschueren S, Monster TB, Meijer K. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: A systematic review and meta-analysis. *J Thromb Haemost* 2016;14:1-11. [Epub ahead of print].

Numerous studies have established that combined hormonal contraceptives (CHCs) increase the risk of venous thromboembolism (VTE), and that women with hereditary thrombophilia are at highest risk. Both the World Health Organization (WHO) and CDC Medical Eligibility Criteria for contraception use place hereditary thrombophilias — antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden (FVL) and prothrombin-G20210A (PT) mutation — as Category 4 (unacceptable health risk). To better evaluate the additional risks associated

with hereditary thrombophilias in users of CHC, van Vlijmen and coauthors performed a meta-analysis using the MEDLINE and EMBASE databases, identifying 12 case-control and three cohort studies of high quality out of an initial literature search with 2,087 hits. The authors classified the baseline severity of a thrombophilia as "mild" (heterozygous for FVL or prothrombin-G20210A mutation) and "severe" (antithrombin deficiency, protein C deficiency, protein S deficiency, double heterozygosity or homozygosity of FVL, and PT mutation). The literature focused on combined oral contraceptive (COC) pills, as the use of patches and rings was not widespread.

The results from the cohort studies provided incidence data, and these were calculated with different control groups for the underlying conditions. The incidence of VTE in COC users with mild thrombophilias (FVL Leiden and PT mutation) was 0.49 (95% confidence interval [CI], 0.18-1.07) to 2.0 (0.3-7.2)/100 pill-years compared to 0.19 (95% CI, 0.07-0.41) to 0.0 (0-5.5)/100 pill-years in COC users without these mutations. The incidence of VTE in COC users with severe (homozygous or double heterozygosity) FVL or PT mutations was 0.86 (0.10-3.11)/100 pill-years compared with 0.19 (0.07-0.41) in COC users without these mutations. The highest incidence was seen in COC users with antithrombin, protein C, or protein S deficiency; 4.3 (1.4-9.7) to 4.62 (2.5-7.9)/100-pill years compared to 0.48 (0.1-1.4) to 0.7 (0.0-3.7)/100 pill-years in non-deficient COC users.

The authors used the incidence values from the control populations in each study to calculate the absolute risk (AR) of VTE in women with thrombophilia. This was considerably higher in COC users with severe thrombophilia (4.3 to 4.6/100 pill-years) than in those with mild thrombophilia (0.49 to 2.0/100 pill-years), respectively. Of interest, the differences in absolute risks were higher in the control group of nonthrombophilic COC users used to evaluate the severe conditions (0.48 to 0.7/100 pill-years) compared to the mild conditions (0.19 to 0.0/100 pill-years). However, these control subjects included relatives of the thrombophilic patients with VTE, suggesting that women with a positive family history of VTE remain at high risk independent of a diagnosed thrombophilia.

The authors concluded that these results support the current practice of discouraging COC use in women with severe hereditary thrombophilia. However, they suggested that the additive VTE risk of mild thrombophilia is only modest, and when no other risk factors (such as a positive family history) are present, COCs could be offered if a reliable alternative is not tolerated.

■ COMMENTARY

Given that estrogen increases the risk of thrombosis, it makes sense for obstetricians and gynecologists to make friends with a hematologist. My local buddy is Tom Deloughery at OHSU. Tom proudly sports a levonorgestrel intrauterine system pin on his lab coat to indicate solidarity with our movement. A great way to solve many problems with coagulopathy.

Like most hematologists, Tom has a mild "allergy" to estrogen. He forwarded this recent manuscript out of the *Journal of Thrombosis and Haemostasis* for my review. The recommendations in this paper that COC may be safely used in women with mild thrombophilias deserves thorough consideration.

The use of COCs remains high in Europe, despite the high incidence of inherited thrombophilias in the northern European population.[1] European women also tend to smoke more than American women, putting them at higher risk.[2] The thrombosis controversy with combined hormonal contraception and the differential effects of various progestins remains an active area of debate, compared to the low level of interest among American clinicians. Given this background, these new recommendations seem surprising.

The overall risk of VTE for women without a positive family history, other identifiable risk factors, or known thrombophilia is low. It is well-established that both pregnancy and estrogen-containing contraceptives increase the risk of VTE.[3] The risk appears to be related to potent synthetic estrogens like ethinyl estradiol and first-pass effects after oral administration of any estrogen, since transdermal administration of estradiol in postmenopausal women does not increase VTE risk.[4]

Inherited thrombophilias not only increase the baseline risk of VTE, they also interact with other known risk factors, such as pregnancy and combined hormonal contraception, to further elevate risk.[1] For this reason, both the CDC and WHO provide a Category 4 (unacceptable risk) rating for CHC in women carrying a known mutation. Although a personal history of VTE also carries a Category 4 recommendation, a family history of VTE in a first-degree relative is only a Category 2 (advantages generally outweigh risks). Routine testing for known thrombophilias in women with a positive family history is not recommended because of high cost and low yield.[5]

The new recommendations from the van Vlijmen paper to consider COC use in women with single mutations for FVL or PT go against WHO and CDC guidelines. I recommend caution when recommendations are based on no new data, and simply reflect the results of a meta-analysis. One of the most important clues to bias is the fact that the incidence rates among non-thrombophilic control COC users in the various papers that contributed to the analysis differed, and were highest, in the "severe" thrombosis studies. It is also important to consider the main findings of the study; the presence of a mild thrombophilia increased the risk of VTE in COC users almost six-fold, while a severe thrombophilia increased the risk of VTE more than seven-fold. One would be hard pressed to defend a six-fold increase as insignificant!

An important side note from this paper is that women with a positive family history of VTE in a first-degree relative are at higher risk of VTE than women without a positive proband *even if they do not carry the same mutation*. This reinforces the importance of positive family history as an important primary risk factor, and, to me, is the most important finding of this paper.

My clinical opinion is to reject the conclusions of van Vlijmen and colleagues, and to continue to follow CDC/WHO recommendations as outlined in the Eligibility Criteria. Although routine testing for known thrombophilias prior to prescription of COCs is not recommended, women with a positive family history deserve careful counseling and consideration of safer alternatives. In all cases, this discussion should be carefully documented. ■

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ABSTRACT & COMMENTARY

What Is the Best Way to Perform a Paracervical Block?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck and a Liletta trainer for Actavis, and she has served on advisory boards for Bayer and Pharmanest.

SYNOPSIS: In this randomized, controlled trial of first-trimester suction D&C procedures, there was no meaningful difference in pain with cervical dilation between a four-site and two-site paracervical block injection nor between waiting three minutes and not waiting after the injection.

SOURCE: Renner RM, Edelman AB, Nichols MD, et al. Refining paracervical block techniques for pain control in first trimester surgical abortion: A randomized controlled noninferiority trial. *Contraception* 2016; May 25 [Epub ahead of print].

This is a two-part, sequential, single-blinded, noninferiority, randomized, controlled trial to compare 1) three-minute wait vs. no wait after paracervical block injection and 2) four-site vs. two-site paracervical block injection. The study was conducted at an outpatient facility in Portland, OR. Healthy adult women requesting surgical abortion who spoke English or Spanish and were less than 11 weeks pregnant by ultrasound dating were enrolled. The paracervical block consisted of 20 mL buffered 1% lidocaine with 2 mL injected at the tenaculum site and the remaining 18 mL injected slowly and deeply in equal amounts paracervically. The four-site block was injected at 2, 4, 8, and 10 o'clock, while the two-site block was injected at 4 and 8 o'clock. All subjects received 2 mg of oral lorazepam and 800 mg of oral ibuprofen at least 30 minutes prior to the procedure. Pain was measured on a 0 to 100 mm visual analog scale (VAS) at speculum insertion, paracervical block injection, cervical dilation, uterine aspiration, and 30 minutes postoperatively. The study was powered to test whether the new intervention (no wait or two-site injection) would be noninferior to the existing practice (wait three minutes or four-site injection) with a pre-specified noninferiority margin of 13 mm on the 0 to 100 mm VAS in terms of the primary outcome: cervical dilation pain.

Overall, 332 women were enrolled (166 in the first part and 166 in the second part) and the majority were in their mid-20s, seven weeks pregnant, and white. The randomized groups were similar in age, gestational age, ethnicity, prior vaginal delivery, prior surgical abortion, and body mass index in both parts of the study. For part one of the study, the mean pain score without waiting and with waiting three minutes was 63 mm ± 24 and 56 mm ± 32, respectively, for cervical dilation. Because the difference was 7.65 mm (95% confidence interval [CI], -1.04, 16.35) and the upper limit crossed the pre-specified non-inferiority margin (13 mm), the results were not significant. Based on this, in part two of the trial, there was no wait time. For part two of the study, the mean pain score with a two-site block compared to a four-site block was 68 mm ± 21 and 60 mm ± 30, respectively, for cervical dilation. The mean difference was 8.65 mm (95% CI, 0.63, 16.67) and, as with part one, was not a statistically or clinically significant difference.

■ COMMENTARY

The paracervical block with lidocaine is a commonly used part of analgesia in many outpatient gynecologic procedures, including suction D&C. Lidocaine is the most common local anesthetic agent used because of its low cost, stability, and low risk of allergic or adverse reactions. It is important to recognize that the block itself causes considerable discomfort.[1] Adding sodium bicarbonate as a buffering agent to lidocaine results in decreased pain during injection (1 mL of 8.4% sodium bicarbonate per 10 mL of local anesthetic).[2] In addition, anecdotally, the smaller the needle size (e.g., 25-gauge vs. 22-gauge), the less pain experienced with injection. Until recently, however, despite its frequent use, the data were conflicting on paracervical block efficacy for cervical dilation pain.[3]

This study is a follow-up to the seminal randomized, controlled trial published by Renner and colleagues in 2012 that proved the efficacy of the paracervical block for pain control. In that trial, the authors randomized 120 women undergoing surgical abortion up to 10 weeks, 6 days' gestation.[4] All women received premedication with 800 mg ibuprofen and 1 mg lorazepam at least 30 minutes prior to aspiration. Women were randomized to receive a 20 mL paracervical block of 1% buffered lidocaine or sham injection. The paracervical block included 2 mL at the 12 o'clock position of the anterior lip of the cervix prior to tenaculum placement, followed by a four-site injection at the 2, 4, 8, and 10 o'clock positions of the cervicovaginal junction. These injections were placed deep (3 cm), with administration of anesthesia while withdrawing. They were also placed slowly over a 60-second period. The sham injection included the administration of 2 mL of 1% buffered lidocaine at the 12 o'clock position of the anterior lip of the cervix prior to tenaculum placement, followed by touching the cervicovaginal junction with a capped needle at the 2, 4, 8, and 10 o'clock positions. Three minutes following administration of paracervical or sham injection, cervical dilation was initiated. The block components were chosen by the results of a Cochrane review the authors conducted indicating that these techniques were the most effective.[3] Pain was measured using a 100 mm VAS. Women reported significantly lower pain scores during cervical dilation (mean 42 mm paracervical block vs. 79 mm sham; $P < 0.001$) and uterine aspiration (mean 63 mm paracervical block vs. 89 mm sham; $P < 0.001$). This was the first randomized, controlled trial with sham injection that demonstrated the efficacy of paracervical block.

The present trial further refines aspects of the paracervical block technique studied in the 2012 trial. The question of whether the three-minute waiting period is necessary and whether four injections are better than two injections was examined. In clinical practice, each gynecologist has his or her preferred method for applying the paracervical block, for example, shallow vs. deep, number of injection sites, size of needle, and volume and type of anesthetic. It is gratifying to know from this study that the three-minute wait did not seem to affect paracervical block efficacy, given that few of us have the patience to wait that long during a procedure. In addition, the number of injection sites did not seem to make a difference in the pain experienced with cervical dilation. The mechanism of action of the paracervical block has been hypothesized partly to be due to tissue distension blocking the nerves. This may explain why a three-minute wait period is not necessary and why a 20 mL block is superior to a 10 mL volume block. In addition, given that the 4 and 8 o'clock positions allow one to reach the nerve plexuses traveling along the uterosacral ligaments, adding sites at 2 and 10 o'clock may not be needed. The paracervical block has been around for more than a century and was originally used for obstetric labor anesthesia. It has now become standard with suction D&C and many other intrauterine procedures, such as hysteroscopy. Further refinements of paracervical block technique supported by evidence are a great addition to the literature. ■

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SPECIAL FEATURE

HPV Vaccines: Why Are We Failing to Vaccinate so Many of Our Adolescents?

By Molly A. Brewer, DVM, MD, MS

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Dr. Brewer reports no financial relationships relevant to this field of study.

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and causes cervical, vaginal, some vulvar, anal, penile, and oropharyngeal cancers. The strongest

association for the development of cancer is with the high-risk HPV (hrHPV) subtypes. Low-risk subtypes are associated with anogenital warts, with HPV 6 and 11 causing 90% of these warts. The link between HPV and cervical cancer was confirmed in the 1990s,[1-5] when epidemiologic studies with advanced molecular detection techniques showed that there was a causative association between cervical cancer and hrHPV infections. Anywhere from 90-100% of paraffin-embedded specimens of cervical cancer were positive for HPV. This was landmark breaking news, since this was the first cancer to be strongly associated with a viral infection.[6-7]

Cervical cancer remains a major public health problem. It is the fourth most common cancer affecting women worldwide, with 528,000 cases in 2012 and 266,000 deaths.[8] It is most prevalent in Asia and Africa, and 85% of the cases occur in less developed countries where access to screening is minimal. The United States has a lower incidence of cervical cancer, with approximately 12,000 cases and 4,100 deaths yearly. However, the cost of following abnormal Pap smears is enormous, and efforts have been made to decrease screening and increase vaccination rates. Given that this cancer is such a world health problem and the cost of screening is large and unreliable, HPV vaccines should substantially reduce the incidence and cost of both screening for and treating hrHPV-related diseases.

The first HPV vaccine was introduced in the United States in 2006, and it contained HPV 6, 11, 16, and 18 (Gardasil-4vHPV). Cervarix (2vHPV), which vaccinates against 16 and 18, was approved in 2009. Both vaccines were approved for males in 2009. Gardasil 9 (9vHPV), which vaccinates against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, was approved in 2014. In 2007, the CDC recommended that all females between the ages of 9-26 years be vaccinated against HPV. Realizing the major health benefit, in 2011, the CDC recommended that all males be vaccinated against HPV. In 2015, the CDC recommended that all women between the ages of 11-26 be vaccinated with one of the three vaccines, and males between ages 11-21 years receive either the 4vHPV or the 9vHPV. Although the vaccine is approved starting at 9 years, the Advisory Committee on Immunization Practices recommends starting vaccinations at age 11.[9] Despite these recommendations, the rates of vaccination remain relatively low compared to other countries. In 2016, the National Cancer Institute-designated cancer centers released a statement that according to a 2015 CDC report, only 40% of girls and 21% of boys in the United States receive the recommended three doses of the HPV vaccine.[10] In 2016, the American Society of Clinical Oncology published a statement on HPV vaccination for cancer prevention. It stated that "Despite the almost certainty that cancers caused by oncogenic HPV types would be dramatically reduced, the use of HPV vaccination is low (36% and 14% of girls and boys, respectively, age 11-13 years have received all three doses)" in 2013.[11] In 2014, the vaccination rates had risen to 60% and 41.7% among girls and boys, respectively. Medicaid patients were almost twice as likely to receive vaccines compared to private insurance.[12] Although no studies have used cervical cancer as the endpoint of vaccine efficacy, there are substantial data showing that vaccination against HPV 16 and 18 offers protection for at least five years in HPV-naïve women against these HPV types.[13] It is extrapolated that just vaccinating against 16 and 18 would reduce the incidence of cervical cancer by as much as 70% as well as reduce the incidence of oropharyngeal cancer, anal cancer, vaginal cancer, vulvar cancer, and penile cancer.[11]

Barriers to HPV vaccination are multiple. Lack of education of parents by healthcare professionals has been the major barrier to vaccination in the United States. Additional barriers include parental concern about sexual activity in their child, safety concerns, and lack of reimbursement. Given that HPV is not a life-threatening condition, there is a long lag-period for manifestation of infections, and the progression to cancer is low even with HPV 16 and 18 infections. Parents have not been adequately educated about the benefits of vaccine.

One study showed that pediatricians discussing vaccination with parents often left discussion of the HPV vaccine last, so parents had the perception that it was less important.[14] Another study showed that pediatricians believed that having to discuss HPV vaccines was burdensome, that they did not have adequate time to discuss the vaccine, and that parents were less supportive of these vaccines. The study showed that a majority of physicians (59%) used a risk-based approach to recommending HPV vaccine, and about half (49%) usually did not recommend same-day vaccination. A substantial minority also reported weaker recommendation practices in the areas of timeliness for males.[15-17] Many other countries have used school-based programs that have resulted in much larger rates of vaccination, such as Australia, which provided a nationally financed program; Rwanda, where free vaccines were provided; and the United Kingdom, where school-based vaccination programs were instituted.[10] These countries have 75-90% vaccination rates compared to the much poorer rates in the United States. The ideal age to vaccinate is before the age of sexual activity so they are HPV naïve. Better immunity occurs in the younger age groups, which may be due partially to lack of exposure to HPV and partially to improved immunity prior to the age of 15 years.

A 2016 study by Paskett et al investigated methods to increase vaccination rates among adolescent girls.[18] The researchers studied groups in Appalachia, OH, which is an area associated with poor vaccine rates and negative attitudes toward the HPV vaccine among parents. This area is considered to be underserved and to have a lower socioeconomic status than other parts of the Midwest. The researchers hypothesized that they could improve vaccine rates by engaging clinics and providers in this effort. Despite extensive educational efforts on multiple occasions for parents and providers, only 17% received vaccination compared to 9% in the comparison group, showing the

challenge of improving the vaccine rate among adolescents. Although this was an improvement, it was not close to what other countries have achieved.

A recent study showed that despite poor vaccine rates, there has been a substantial reduction in the rate of HPV infections in the United States, with 11.5-4.3% reduction in the 4vHPV women ages 14-19 years and 18.5-12.1% decrease in women ages 20-24 years. Despite the relatively low vaccination rate, there has been a substantial reduction in the hrHPV infections.[19] In addition, the 9vHPV vaccine, which is more expensive than the 4vHPV and 2vHPV vaccines, was cost effective when modeled nationally.[19] They estimated that using 2vHPV and 4vHPV would reduce the cervical cancer incidence by 63% and death rate by 43%. Switching to the 9vHPV is hypothesized to reduce the incidence by 73% and the death rate by 49%. Vaccinating 11% more of the population with the 2vHPV or 4vHPV would cost $2.7 billion more than increasing this coverage with the 9vHPV vaccine.

■ COMMENTARY

The ability to prevent cancer is truly a new phenomenon. In the 1980s and 1990s, there was substantial work to link HPV to cervical cancer and precancer, and in the 2000s, there was substantial work that linked high-risk HPV, particularly 16 and 18, to the highest risk of cancer. There are now three vaccines that provide excellent protection against both 16 and 18 as well as 9vHPV, which is estimated to reduce the incidence of cervical cancer with a lower cost than the first two vaccines developed.

Why are all young people between the ages of 9 and 15 years not being vaccinated? The most common reason is physicians are not giving parents adequate information about the importance of the vaccine and the long-term reduction in morbidity. Pediatricians are the most common physicians to care for these young people, and they often are overburdened with sick patients and long hours. Putting this vaccine program into schools has been the most successful type of program worldwide, yet there was large pushback from parents in states that tried to mandate the vaccine. We need to better educate parents that preventing the diseases associated with hrHPV will keep their children healthier into adulthood. As a nation, we are afraid of discussing a sexually transmitted disease with our adolescents. It's time to work harder educating about this preventable disease. ■

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CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. **In the *Lancet* study, patients in the immediate delivery group had higher rates of all but which of the following outcomes?**
   a. Cesarean sections
   b. Respiratory distress syndrome
   c. Need for antibiotics
   d. Long stays in the NICU
2. **Given the findings from the van Vlijmen study, which of the following is *not* true for women with a positive family history of unprovoked VTE in a first degree relative?**
   a. All women of northern European background should have a screening test for the Factor V Leiden mutation before any hormonal contraception prescription.
   b. Women with relatives who have "mild" thrombophilias such as heterozygotes for Factor V Leiden can safely use COCs.
   c. The CDC medical eligibility criteria recommends that benefits of COC use outweigh potential risks.
   d. A levonorgestrel-containing combined pill would be appropriate without additional testing.
3. **In the study by Renner et al, a four-site paracervical injection was superior to a two-site paracervical injection.**
   a. True
   b. False
4. **Vaccinating with the 9vHPV protects against which of the following?**
   a. Only HPV 16 and 18
   b. Only HPV 6 and 11
   c. Only HPV 6, 11, 16, 18
   d. HPV 6, 11, 16, 18, 31, 33, 45, 52, 58

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

[IN FUTURE ISSUES]

PCOS and Hormonal Contraception: A Tale of Two Syndromes?