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Evidence-based commentaries on women's reproductive health

SPECIAL FEATURE

New Prescription Drug Labeling for Pregnant and Nursing Women

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Dr. Lim and Dr. Thompson report no financial relationships relevant to this field of study.

On average in the United States, there are more than 6 million pregnancies annually, and an expecting mother or woman will take three to five prescription medications while pregnant.[1] To better assist obstetricians and other healthcare providers with assessing drug benefits and risks for pregnant patients and nursing mothers taking medications, the FDA has updated the requirements for the pregnancy and lactation sections of drug labeling. The rule addresses shortcomings with the current prescription drug labeling information, and requires content and format changes to the requirements under the Physician Labeling Rule (PLR). Overall, the changes allow pregnant women and their healthcare providers to be better informed about the risks and benefits of medications while pregnant or nursing. The new Pregnancy and Lactation Labeling Rule (PLLR) went into effect in June 2015 and is being phased in over the next three to five years.

LABELING THROUGH THE YEARS

Prescription drug labeling is a communication tool. Its principal objective is to make available to healthcare providers the detailed prescribing information necessary for the safe and effective use of a drug, and to do so in a manner that is clear and useful when counseling patients about prescriptions.

Regulations on labeling for human prescription drug use during pregnancy, labor, and delivery and by nursing mothers were issued originally in 1979. In May 2008, the FDA published rules on the content and format of labeling for human prescription drug and biologic products. Nearly 30 years after the codification of the first regulation that provided standardized guidance to healthcare professionals about the use of prescription drugs in pregnant women and nursing mothers, the FDA proposed to eliminate the pregnancy categories because they are

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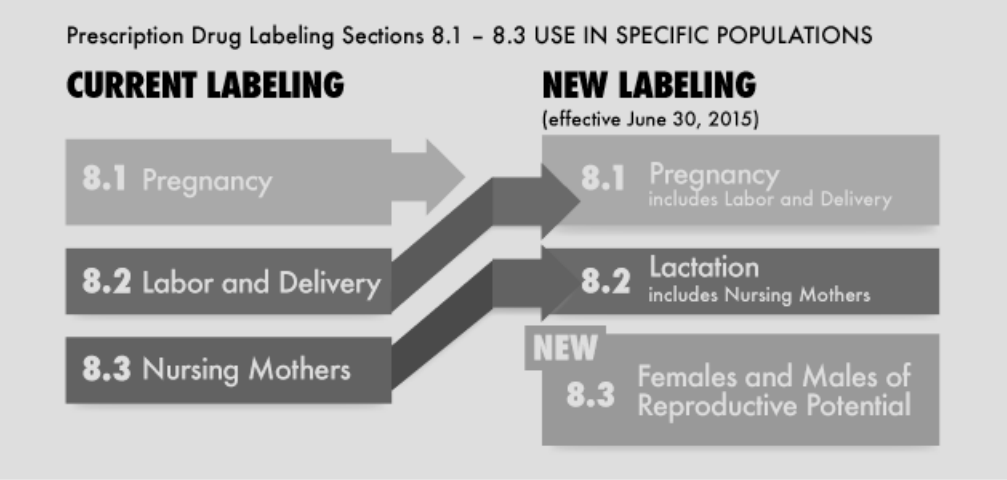

often viewed as "… confusing and overly simplistic and, therefore, not adequate to effectively communicate risk of reproductive and developmental toxicity."[2] In December 2014, the FDA published an update known as the PLLR. The new requirements went into effect in June 2015.

The following questions and answers provide information that may be helpful to obstetricians and other prescribers about medication use while pregnant or nursing.

Q. What are key changes to the prescribing information that went into effect in June 2015?
The former subsections of the labeling rule (Pregnancy, Labor and Delivery, and Nursing Mothers) will be replaced by three new subsections entitled Pregnancy, Lactation, and Females and Males of Reproductive Potential. Table 1 outlines the content of these new subsections. The PLLR also requires the removal of the pregnancy categories – A, B, C, D, and X – from all prescription drug product labeling. Additionally, the PLLR requires the labeling to be updated as new information becomes available.

Q. Why did the FDA make these changes?
Prescribing decisions during pregnancy and lactation are highly individualized and involve complex maternal, fetal, and infant risk–benefit considerations. The pregnancy categories in drug labeling often were viewed as confusing and overly simplistic and didn't effectively communicate the risk a drug may have during pregnancy. The FDA believes that a narrative structure is best able to capture and convey the potential risks of drug exposure.

Q. Which medications are affected?
All prescription drugs and biologic products that follow the PLR (those approved since June 30, 2001) will be affected. Prescription drugs and biologic products submitted for approval on or after June 30, 2015, will use the new format, while labeling for prescription drugs approved June 30, 2001 through June 29, 2015, will be phased-in. For products approved prior to June 30, 2001, manufacturers are required to remove the pregnancy category within three years of the effective date of the final rule. Labeling for over-the-counter (OTC) medicines will not change; OTC drug products are not affected by the final rule.

Q. What is a pregnancy exposure registry and why does the FDA's Office of Women's Health keep a list?
A pregnancy exposure registry is an observational study that collects health information from women who take prescription drugs or vaccines when they are pregnant. Pregnancy exposure registries maintain data on the effects of approved drugs that are prescribed to and used by pregnant women. The FDA does not conduct any studies collected in the pregnancy exposure registries, and does not endorse any registry, but may recommend or require that a drug company implement a pregnancy exposure registry based on certain criteria. The FDA's Office of Women's Health maintains a list of registries, which is posted on the FDA's website at: http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm. Enrolling in a pregnancy exposure registry can help improve safety information for medicines used during pregnancy and can be used to update drug labeling.

Table 1: Label Changes by Subsection

Subsection	Subheadings	Description
8.1 Pregnancy	Pregnancy Exposure Registry (if applicable)	• Information (including contact information) regarding a pregnancy exposure registry that monitors pregnancy outcomes
	Risk Summary	• Statement that the drug is contraindicated during pregnancy (if applicable) • Risk statement based on human data • Risk statement based on animal data • Risk statement based on pharmacology (if applicable) • Background birth defects and miscarriage rates
	Clinical Considerations (if applicable)	• Disease-associated maternal and/or embryo/fetal risk • Dose adjustments during pregnancy and the postpartum period • Maternal adverse reactions • Fetal/neonatal adverse reactions • Labor or delivery
	Data (if applicable)	• Data on which the Risk Summary and Clinical Considerations are based
8.2 Lactation	Risk Summary	• State that the drug is contraindicated during lactation (if applicable) • Presence of drug in human milk • Effects of drug on the breastfed child • Effects of drug on milk production/excretion • Risk and benefit statement (if applicable)
	Clinical Considerations (if applicable)	• Minimizing exposure to the breastfed infant • Monitoring the breastfed infant for adverse reactions
	Data (if applicable)	• Data on which the Risk Summary and Clinical Considerations are based
8.3 Females and Males of Reproductive Potential	Pregnancy Testing (if applicable)	• Recommendations or requirements for pregnancy testing before, during, or after drug therapy
	Contraception (if applicable)	• Recommendations or requirements for contraception use before, during, or after drug therapy
	Infertility (if applicable)	• Human and/or animal data suggesting drug-associated effects on fertility

Q. If the labeling must be continuously updated as more information becomes available, what is the best way for me to obtain up-to-date information?
The drug labeling information for medications marketed in the United States can be found on FDA's Drugs@FDA at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm and the National Library of Medicine's DailyMed at http://dailymed.nlm.nih.gov.

The changes to the regulations for the content and format of the Pregnancy subsection in prescription drug labeling attempt to address the lack of information available to healthcare professionals, pregnant women, and nursing mothers. The pregnancy categories A, B, C, D, and X that were once a necessary reference and a fairly accurate guide now appear to be an archaic tool given the advances in medicine and data collection. Not only does new pregnancy labeling assist healthcare professionals with assessing risk vs. benefit and subsequent counseling, it also allows women to make informed and educated decisions for themselves and their children. ■

REFERENCES

1. Barbor M. Medscape Medical News from the American Society of Health-System Pharmacists (ASHP) 2015 Midyear Clinical Meeting. FDA Issues New Drug Safety Information for Pharmacists. Published December 10, 2015.
2. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, 2008.

ABSTRACT & COMMENTARY

Smoking Cessation and Preterm Birth

By John C. Hobbins, MD

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

SYNOPSIS: A study using Ohio state birth data showed that women who stopped smoking by the end of the first trimester had the same rates of preterm birth as nonsmokers. Women who stopped in the second trimester had preterm birth rates similar to those who smoked all the way through pregnancy.

SOURCE: Moore E, Blatt K, Chen A, et al. Relationship of trimester-specific smoking patterns and risk of preterm birth. *Am J Obstet Gynecol* 2016;215:109.e1-6.

Even though fewer people are smoking now than 10 years ago, there still remains a formidable number of individuals who, despite being aware of the dangers of smoking, continue to light up. A previous *Alert* touched on how smoking fallout from passive exposure to cigarette smoke can have a detrimental effect on non-smoking pregnant women.[1]

One reason about 11.5% of pregnant women continue to smoke is that it is hard to quit. Yet, as the featured study suggests, doing so can have significant benefit if undertaken early in pregnancy.

[The earlier a pregnant woman quits smoking, the smaller her chance of delivering a premature baby.]

In Ohio, the overall rate of smoking in pregnancy is 23%. A group of investigators, having a ready population to study, set out to determine if there was benefit to cessation in early pregnancy with regard to one outcome variable: preterm birth (PTB). They examined the Ohio birth records of 913,757 patients from 2006 through 2012, 25% of whom were smokers. They broke the smoking patients into four groups: 1) early quitters, who only smoked preconception; 2) first trimester quitters; 3) second trimester quitters; and 4) those who smoked throughout pregnancy. Data regarding preterm birth were compared to data from nonsmokers. The authors attempted to correct for confounding influences.

The early quitters had a PTB rate that was no different than nonsmokers; in the first trimester quitters, the PTB rate less than 37 weeks was not significantly higher than nonsmokers but, strangely, it was higher for PTB below 28 weeks (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.03-1.40). Quitting late resulted in the highest rate of PTB prior to 37 weeks, compared with nonsmokers (OR, 1.70; 95% CI, 1.60-1.80), even after accounting for confounding variables. However, the rate was not significantly different than if they smoked throughout pregnancy. The most dramatic finding was that quitting late was associated with the greatest increase in PTB at less than 37 weeks, whatever the cause (65% increase in spontaneous labor and a 78% increase in indicated intervention).

■ COMMENTARY

One can conclude from this study that the women who were able to stop smoking by the end of the first trimester had an excellent chance of avoiding cigarette-associated preterm birth. Hopefully, this will provide further evidence during counseling to motivate patients to stop smoking.

The ill effects of smoking are not based on nicotine alone. Smokers have high levels of carboxyhemoglobin, which can affect transfer of oxygen and nutrients across the placenta, giving new meaning to the term "placental barrier." Quitting late in pregnancy has little effect on the one outcome variable studied here, preterm birth, but is borne out indirectly by the observation that many patients who have stopped smoking at varying intervals after the first trimester often display ultrasound signs of "premature placental senescence" (increased areas of echogenicity) as early as 32 weeks.

From this study it seems that the earlier a woman quits smoking, the smaller her chance of delivering a premature baby. Another study,[2] feature in the earlier *Alert*, has shown that those who do stop early or, interestingly, have been subjected to passive cigarette smoke (as measured by plasma cotinine levels) are at higher risk for pre-eclampsia compared with non-smokers. ■

REFERENCES

1. Hobbins JC. Passive smoking exposure and preeclampsia. *OB/GYN Clinical Alert* 2014;31:21-22.
2. Luo ZC, Julien P, Wei SQ, et al. Plasma cotinine indicates an increased risk of preeclampsia in previous and passive smokers. *Am J Obstet Gynecol* 2014;210:232.e1-5.

ABSTRACT & COMMENTARY

Should Perimenopausal Women Consider Estrogen Therapy?

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen reports he is a consultant for Teva Pharmaceuticals, Microchips, and Evofem; and is a consultant for and receives grant research support from Bayer Healthcare, Merck, Agile Pharm, Population Council, AbbVie, ContraMed, and FHI360; and receives grant/research support from HRA Pharma and Medicines 360.

SYNOPSIS: A population-based study found that premenopausal women with low ovarian reserve, as determined by low levels of anti-Müllerian hormone, have unfavorable cardiovascular disease profiles.

SOURCE: de Kat AC, Verschuren WMM, Eijkemans MJC, et al. The association of low ovarian reserve with cardiovascular disease risk: A cross-sectional population-based study. *Hum Reprod* 2016;31:1866-1874.

The available literature suggests that early initiation of hormone replacement therapy (HRT) may reduce cardiovascular disease (CVD).[1] Since age is also a risk factor for CVD, the critical window for early intervention is a hot topic. The Doetinchem Cohort Study is a population-based cohort study from the Netherlands established to study risk factors for chronic disease. Participants answered questions about lifestyle determinants, reproductive characteristics, and general health, and also underwent biometric and laboratory assessments. To determine whether anti-Müllerian hormone (AMH) levels were associated with other risk factors for CVD, the authors evaluated premenopausal women (one or more menstruations in the past year) who participated in the cohort between 1993 to 1997 (n = 2,729). Of these, 2,338 had stored serum samples available for analysis. The lower limit of quantification of AMH in the ELISA assay used by the investigators was 0.16 ng/mL. The investigators assessed CVD risk using the metabolic risk score (total number of risk factors present: waist circumference ≥ 80 cm, hypertension, HDL cholesterol < 39 mg/mL, total cholesterol > 217 mg/mL, use of lipid-lowering drugs). Baseline characteristics included a number of potential confounders: age, current oral contraceptive use, current smoking, body mass index, parity, cycle regularity, socioeconomic status, estrogen use (at the time of follow-up), and pregnancy (at the time of follow-up). The presence of polycystic ovary syndrome was considered a potential effect modifier and defined as a self-report of irregular cycles in combination with an AMH > 4.7 ng/mL.

The age range of the study population was 20-57 years. Overall, the relationship between AMH levels and CVD risk factors was nonlinear. Women with AMH levels at or below the limit of quantification (0.16 ng/mL) had more metabolic risk factors (relative risk, 0.11; 95% confidence interval, 0.01-0.21) than women with AMH ≥ 0.16 ng/mL. Individual CVD risk factor levels were not associated with low AMH levels.

■ COMMENTARY

Is a high-risk cardiovascular profile determined during perimenopause? Evidence is accumulating that the key failure of the Women's Health Initiative study was the recruitment of an asymptomatic and older (approximately 10 years postmenopausal) cohort of women with baseline CVD. Early initiation of HRT may prevent the development of atherosclerotic plaque while later administration may exacerbate risk by introducing a prothrombotic effect in women with existing plaque. Evidence in support of this conclusion include the Estrogen in Prevention of Atherosclerosis Trial (EPAT), which showed a reduction of atherosclerosis progression in postmenopausal women without coronary heart disease who were treated with oral estradiol, and the Women's Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), which found no benefit of estrogen therapy in women with existing coronary lesions.[2] The Early versus Late Intervention Trial with Estradiol (ELITE) study found that initiation of oral estradiol and vaginal micronized progesterone within six years of onset of menopause reduced the progression of atherosclerosis, an effect not seen when therapy was initiated after 10 years.[3]

Moving this discussion forward to women in the perimenopause is hazardous. First, the perimenopause is difficult to rigorously define. Ovarian reserve and estrogen levels may not correlate. Henry et al followed markers of ovarian function in premenopausal women before and following chemotherapy.[4] Although AMH declined from 1.95 to 0.23 ng/mL and follicle-stimulating hormone (FSH) increased (7.6 to 32.6 mIU/mL) one year post-chemotherapy, estradiol levels remained stable (baseline 79.1 to 92.5 pg/mL post-treatment). With the court of public opinion still profiling hormonal therapy as risky, expanding the discussion of early initiation of HRT into the premenopausal years will require a convincing argument.

Although the Doetinchem Cohort Study demonstrates a modest increase in the metabolic risk score for perimenopausal women with very low AMH levels, the results should be evaluated with caution. First, the overall magnitude of the effect is small, about one-tenth of a risk factor point measured on a five-point scale. Although the authors stated that the effect size was larger in the youngest women with low AMH, this was not statistically significant and the data are not shown. Also, no single CVD risk factor was associated with low AMH levels, suggesting weaknesses in the methodology to elucidate a causal pathway using this outcome. Whether these small differences in the metabolic risk score affect long-term health have not been validated.

On a positive note, the results do follow on other studies that have identified unfavorable lipid profiles in premenopausal women with low AMH levels[5] or elevated FSH and low antral follicle counts.[6]

While we wait for the science to settle, these preliminary results provide an opportunity to consider estrogen effects across a woman's life. Estrogens exert a favorable effect on vascular endothelium, which reduces the risk of atherosclerotic plaque formation.[7] As estrogen levels decline, this protection diminishes, and plaque accumulates, particularly in women with unfavorable lipid profiles and other cardiovascular risk factors. Consider also that the ovarian follicle represents a net lipid-consuming organ. During a natural cycle, steroid hormone production contributes to a net drop in circulating lipid levels; about a 5% decline occurs in the luteal phase during the massive synthesis of progesterone.[8] All of this changes as cycles become irregular and then stop. So the effect on lipids is complicated, and represents ovarian and extra-ovarian metabolism, and direct hormonal effects.

The current data do not support a recommendation to treat perimenopausal women with hormonal therapy. Demonstrating that premenopausal initiation of HRT reduces CVD will require a large, prospective clinical trial, so don't hold your breath awaiting the results. However, many women who present with symptoms of hot flashes or estrogen withdrawal headache benefit from estrogen therapy. Given that studies of early menopausal treatment women with HRT demonstrate benefit, extending treatment to symptomatic perimenopausal women may provide a secondary cardiovascular health benefit as well. ■

REFERENCES

1. Harman SM, Vittinghoff E, Brinton EA, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. *Am J Med* 2011;124:199-205.
2. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-953.
3. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;374:1221-1231.
4. Henry NL, Xia R, Schott AF, et al. Prediction of postchemotherapy ovarian function using markers of ovarian reserve. *Oncologist* 2014;19:68-74.
5. Tehrani FR, Erfani H, Cheraghi L, et al. Lipid profiles and ovarian reserve status: A longitudinal study. *Hum Reprod* 2014;29:2522-2529.
6. Verit FF, Keskin S, Omer B, et al. Is there any relationship between cardiovascular risk markers and young women with diminished ovarian reserve? *Gynecol Endocrinol* 2014;30:697-700.
7. Miller VM, Clarkson TB, Harman SM, et al. Women, hormones, and clinical trials: A beginning, not an end. *J Appl Physiol* 2005;99:381-383.
8. Barnett JB, Woods MN, Lamon-Fava S, et al. Plasma lipid and lipoprotein levels during the follicular and luteal phases of the menstrual cycle. *J Clin Endocrinol Metab* 2004;89:776-782.

ABSTRACT & COMMENTARY

Can the Human Papillomavirus Vaccine Cure Cervical Dysplasia?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, and is on the advisory boards for Bayer and Pharmanest.

SYNOPSIS: In this randomized, controlled trial, the human papillomavirus (HPV) 16/18 vaccine did not hasten resolution of existing oncogenic HPV infections nor prevent persistent HPV 16/18 associated infection and cervical dysplasia recurrence after loop electrosurgical excisional procedure treatment.

SOURCE: Hildesheim A, Gonzalez P, Kreimer AR, et al. Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment. *Am J Obstet Gynecol* 2016;215:212.e1-15.

This is a re-analysis of a randomized, controlled trial conducted in Costa Rica among 7,466 women 18-25 years of age that evaluated the efficacy of the human papilloma virus (HPV) 16/18 vaccine (Cervarix). Women were randomized to either the HPV 16/18 vaccine or the hepatitis A vaccine and were followed

annually with referral to colposcopy for high-grade dysplasia and/or persistent low-grade dysplasia, and treatment by loop electrosurgical excisional procedure (LEEP) when indicated. This reanalysis included two groups of women: 1) 1,711 participants who, at entry, were infected with one or more of 12 oncogenic HPV types and who were randomized, vaccinated, and followed for a median of 56.7 months; and 2) 311 participants who were randomized, vaccinated, and at some point during follow-up received a LEEP, and followed for a median of 27.3 months. HPV infection was chosen as the unit of analysis, and 31.4% of women had more than one HPV type at enrollment. HPV infection was divided into the following categories: 1) HPV 16 and/or 18; 2) HPV 31 and/or 33 and/or 45, which are HPV types for which evidence of cross-protection with the HPV 16/18 vaccine has been documented; and 3) other oncogenic HPV types. The outcomes for the evaluation of women with prevalent infections at enrollment included type-specific viral clearance and development of cervical lesions. The outcomes for the evaluation of women treated by LEEP were HPV infection, persistent HPV infection (detecting a specific type at two or more consecutive visits after treatment), and development of cervical lesions. Vaccine efficacy was reported as a percent reduction or increase in the outcome rates observed when the HPV vaccine arm was compared to the control hepatitis A vaccine arm.

Among women with oncogenic HPV infection at enrollment, there was no evidence that the HPV vaccine compared to control altered resolution of existing HPV infections. For example, among infected women without existing cervical dysplasia, the efficacy of the vaccine was -5.4% (95% confidence interval [CI], -19 to 10) for clearance, -15.5% (95% CI, -86 to 28) for progression to CIN 1+, and 0.3% (95% CI, -69 to 41) for progression to CIN 2. Among women who underwent LEEP procedures, it was found that, after treatment, 34.1% of the 311 women had one or more oncogenic HPV infections detected and 1.6% had CIN 2+ detected. Among these women, approximately 70% of infections were new HPV infections and 20% of the CIN 2+ lesions were the result of new HPV infections that were absent before treatment. There was no effect of vaccination on persistent HPV 16/18 infections or HPV 16/18 associated cytologic/histologic lesions after LEEP.

■ COMMENTARY

The HPV vaccine is highly effective in preventing new HPV infection in girls and women naïve to the virus and, thus, preventing HPV-related dysplasia. The HPV vaccines available in the United States include Gardasil-4 (6, 11, 16, 18), Cervarix-2 (16, 18), and Gardasil-9 (6, 11, 18, 31, 33, 45, 52, 28). The HPV vaccine is recommended for females between the ages of 11 and 26 and males between the ages of 11 and 21 by the Centers for Disease Control and Prevention.[1] The mechanism of action of the various HPV vaccines is to induce antibodies against the L1 protein in HPV that then neutralize the ability of HPV to infect cells. Whether there is a secondary vaccine effect on existing infected cells whereby the antibodies reduce spread of virus to new cells or the development of a cell-mediated immunity against L1, which promotes clearance of virus in infected cells, is controversial. The authors of this study previously had reported shorter-term results on a smaller number of women that the HPV 16/18 vaccine did not have any effect of clearing existing infections.[2] Now they have expanded that analysis in a larger study with longer follow-up, adding an evaluation of the effect of vaccination on the progression of prevalent infections and after LEEP treatment.

This well-done study falls short only in the evaluation of the women who underwent LEEP, as some of the categories had very small numbers and, thus, large confidence intervals. Nevertheless, in the main analysis, the data are convincing that the HPV vaccine does not hasten resolution of existing infections or prevent progression to cervical dysplasia. Furthermore, the vaccine does not reduce post-LEEP infections or dysplasia. On a positive note, there was some suggestion that the vaccine may protect against new infections post-LEEP.

So what are the implications of this study? Current recommendations allow for HPV vaccination in women who have known HPV infections in the hopes that they may be protected from strains they have not been exposed to yet.[3] This makes more sense to me now that Gardasil-9 is available. Nevertheless, this study further reinforces the fact that we should be vaccinating young men and women before the onset of sexual activity to reap the full benefits of vaccination. By the time the patient presents for colposcopy, the benefit of vaccination is small, as this study shows. Unfortunately, current vaccination rates in the United States are low, with the latest estimates being 50% of males have started the vaccine series with 28% completing three doses and 63% of females have started the vaccine series with 42% completing three doses.[4] This is compared to approximately 87% of adolescents having received at least one Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) vaccine. Although obstetrician-gynecologists usually do not see females in the preteen age group, we can work to support HPV vaccination efforts in the patients we do see, speaking to mothers about the importance of vaccination for their daughters and sons, as well as supporting efforts to confront misconceptions regarding the vaccine in our schools and communities. ■

REFERENCES

1. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2014;63:1-30.
2. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: A randomized trial. *JAMA* 2007;298;743-753.

3. ACOG Committee Opinion Number 641. Human papillomavirus vaccination. September 2015.
4. Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years — United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65;850-858.

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CME/CE QUESTIONS

1. **In the Moore et al study, women who quit smoking by the end of the first trimester had a rate of preterm birth that was:**
   a. higher than non-smokers.
   b. the same as those who quit in the second trimester.
   c. the same as those who smoked throughout pregnancy.
   d. no higher than non-smokers

2. **A low ovarian reserve measured by an anti-Müllerian hormone level < 0.16 ng/mL was associated with:**
   a. a two-fold increase in the risk of cardiovascular mortality.
   b. a 50% reduction in risk of myocardial infarction.
   c. a body mass index > 30 kg/m^2 and type 2 diabetes
   d. an 11% increase in the cardiovascular disease risk factor score.

3. **In the study by Hildesheim et al, the HPV 16/18 vaccine was shown to promote clearance of existing HPV 16/18 infections.**
   a. True
   b. False

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]

HPV Testing: An Approach Whose Time Has Come

What's the Buzz About Measuring Ovarian Reserve?