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OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

# Hormonal Contraception: A Risk Factor for Depression?

*By Jeffrey T. Jensen, MD, MPH, Editor*

SYNOPSIS: A population-based study suggests that hormonal contraception increases the risk of treatment for depression, but bias provides a more likely explanation for the association.

SOURCE: Skovlund CW, Morch LS, Kessing LV, Lidegaard O. Association of hormonal contraception with depression. *JAMA Psychiatry* 2016 Sept. 28. doi: 10.1001/jamapsychiatry.2016.2387. [Epub ahead of print].

Little objective information is available to assess the relationship between mood disorders and hormonal contraception. In this manuscript, the group headed by Øjvind Lidegaard used the Danish Sex Hormone Register Study, a nationwide cohort study that includes all women living in Denmark, to evaluate the question. The database links health records and diagnoses to prescriptions. To explore the association of hormonal contraception to depression, the authors used the database to identify incident diagnoses of depression in women aged 15 to 34 years from Jan. 1, 2000, to Dec. 31, 2013. Women with a prior history of depression or a medical contraindication to hormonal contraception were excluded, as were those with a history of cancer or infertility. The authors defined hormonal contraception use as current or recent (within six months) use to categorize women who may have discontinued hormonal contraceptive due to depression as users. The reference group of nonusers included never users and former users (discontinued more than six months). The primary outcome was first diagnosis of depression or prescription of an antidepressant medication in users vs. non-users of hormonal contraception.

After exclusions, the study population included 1,061,997 women with 6,832,938 person-years of observation. Of these, 55.5% were current or recent users of hormonal contraception. A total of 133,178 first prescriptions for antidepressants and 23,077 first diagnoses of depression were identified in the cohort. An increased risk of first use of antidepressants was seen in users of all methods of hormonal contraception: combined oral contraceptives (relative risk [RR], 1.23; 95% confidence interval [CI], 1.22-1.25); progestin-only pills (RR, 1.3; 95% CI, 1.27-1.40); transdermal patch (RR, 2.0; 95% CI, 1.76-2.18); vaginal ring (RR, 1.6;

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95% CI, 1.55-1.69); etonogestrel implant (RR, 2.1; 95% CI, 2.01-2.24); levonorgestrel intrauterine system (RR, 1.4; 95% CI, 1.31-1.42); and medroxyprogesterone acetate depot (RR, 2.7; 95% CI, 2.45-2.87). They found similar associations with a first diagnosis of depression.

Of concern, the authors also noted a higher risk of first use of an antidepressant associated with hormonal contraception among adolescents (15-19 years) compared to older women. They also found that the overall risk peaked after six months of use (RR, 1.4; 95% CI, 1.34-1.46) but then declined. Long-term use of hormonal contraception did not increase risk of first use of an antidepressant; the authors attributed this to attrition of susceptibles.

To further explore these relationships, the authors performed sensitivity analyses comparing the first use of an antidepressant in the same women before and one year after starting use of hormonal contraceptives. This strengthened the elevated overall risk (RR, 1.6; 95% CI, 1.58-1.69) with the highest risk in younger women (RR, 1.8; 95% CI, 1.72-1.88).

The authors concluded that depression is a potential adverse effect of hormonal contraceptive use.

## ■ COMMENTARY

As you ponder these results, consider two interesting demographic observations. First, maternal mortality is on the rise in the United States. The estimated maternal mortality rate for 48 states and the District of Columbia increased from 2000 to 2014.[1] In the other direction, and for the first time in my life, we see a sustained decrease in both teen pregnancy and unintended pregnancy that began in 2008.[2] The widespread use of hormonal contraception, and in particular highly effective long-acting reversible contraception methods, explains the success in pregnancy reduction, with health disparities a likely contributor to mortality. Highly effective reversible contraception levels the playing field for women and allows them to achieve their full potential. The most effective methods are hormonal.

Since hormonal methods are used widely, any health benefits or risks associated with their use deserve serious attention. Unfortunately, the media disproportionately report studies suggesting potential health risks and remain silent on benefits.[3] Thus, you may have seen news stories or fielded patient calls related to this new manuscript by the Lidegaard group. Before accepting the conclusion of a link between hormonal contraception and depression, consider the following.

The Danish National Database is the gift that keeps on providing concerning information about the safety of hormonal contraception. This comprehensive population-based database provides substantial strengths for epidemiologic study, in particular the linkage of prescription data to clinical outcomes. The large number of individuals in the database yields precise estimates of risk with tight confidence intervals irresistible to journals. But, as I have pointed out in prior reviews, bias must be considered as an explanation of any epidemiologic finding. For example, the numerous publications from Lidegaard using this database that suggest an increased risk of venous thrombosis associated with drospirenone and desogestrel-containing combined pills have not been confirmed by true prospective studies.[4,5] Major limitations of the Danish Database include the absence of baseline information concerning important confounders, and the inability to control for prescription bias and the healthy user effect.

The current study on depression puts a new twist on this. The overall effect appears sound and free of prescription bias, as the elevated risk occurred with any use of hormonal contraception. Lidegaard boldly asserted that the sensitivity analysis that compared women to themselves before and after a prescription for hormonal contraception "controlled for all potential confounders, which did not change during the observation period and eliminated healthy-user bias." However, women who accept the use of hormonal contraception likely differ from nonusers. Most importantly, those who use a prescription medication like hormonal contraception may be more likely to use another prescription medicine, like an antidepressant, or to seek medical care for depression. Furthermore, these attitudes may change over time. Even a small tendency toward this could bias the results. Do not be misled by the tight confidence intervals and statistically significant effect for risk estimated in this range of "weak association."

What is a weak association? A recent publication by Grimes provides an excellent review for those interested in evaluating database studies.[6] The most important consideration is strength of association. For cohort studies like the Danish Database, the lower limit of discrimination for a

causal effect is a RR of 2.0. Bias provides the most likely explanation for RRs below 2. Only a properly conducted randomized, controlled trial free of bias can adequately assess smaller effects. Few of the associations in this paper cross the threshold so by definition are weak and suspicious. Absence of a clear dose response also is puzzling (e.g., lowest risk for highest dose levonorgestrel combined oral contraceptives [1.3] with higher risks for the levonorgestrel progestin-only pill [1.7] and levonorgestrel intrauterine system [1.4]).

But what about the transdermal patch (RR 2.1), the implant (2.1), and depo medroxyprogesterone acetate (DMPA, 2.7) with risk estimates that cross this threshold? I suspect misclassification bias, as the study design does not account for prior use. Thus, we cannot determine if a diagnosis of depression or prescription correlated with the current method, the prior method, or unrelated factors. Consider that Denmark is ground zero for the oral contraception thrombosis controversy. Danish providers and many patients are strongly influenced by the first-line recommendation promoted heavily by Lidegaard to use only levonorgestrel pills for initial starts, switching only for intolerance. Pills also represent the most common method prescribed to teens. It would not be surprising if users experiencing mood disturbances might switch to a new method (particularly an estrogen-free method) to control symptoms prior to receiving a diagnosis or treatment for depression. Also, the limited use of DMPA, implants, and the patch suggests that users of these methods may differ in many unmeasured characteristics that could influence risk of depression.

To be fair, Lidegaard performed a sensitivity analysis to address the issue of unmeasured confounding. This included only those women who started hormonal contraception during the study period, comparing the incidence of depression (or first prescription for antidepressants) within one year after initiation of hormonal contraception with the incidence rate during the time prior to hormonal contraceptive use. Overall, this strengthened the relationship observed in the cohort. However, the authors' claim that this "controlled for all potential confounders" and "eliminated healthy-user bias" deserves careful consideration. Although this approach does control for stable physical attributes, it does not take into account psychological and social factors that change over time and influence risk of depression. A fatal flaw of the analysis is the failure to account for the correlation between first use of hormonal contraception and initiation of sexual activity, a potentially emotionally vulnerable time.[7] That the sensitivity analysis supports the main analysis simply demonstrates the problem with precision and accuracy. You can hit the same spot on the target every time with great precision, but always miss the bull's-eye.

Depression represents an important health concern. Many women report mood changes while on hormonal contraception, and all of us can think of patients who improved after discontinuation. Most of us also have prescribed hormonal contraception to women with premenstrual dysphoric disorder with improvement, a position supported by a recent Cochrane review.[8] More research obviously is needed. Unfortunately, this study may discourage vulnerable women from using a hormonal contraceptive. I worry about this, as research supports a link between unintended pregnancy and depression.[9] As clinicians, we need to provide an open discussion about the risks and benefits of hormonal methods. No one method will meet the needs of all women. In my experience,

[As clinicians, we need to provide an open discussion about the risks and benefits of hormonal methods. A frank discussion of mood disorders in a welcoming clinic environment will help ensure that patients receive appropriate guidance in selecting an appropriate new method of birth control.]

women experiencing a mood disturbance while using hormonal contraception will discontinue with or without medical advice. A frank discussion of mood disorders in a welcoming clinic environment will help ensure that the patient receives appropriate guidance in selecting an appropriate new method of birth control. ■

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ABSTRACT & COMMENTARY

# HPV Testing: An Approach Whose Time Has Come?

*By Molly A. Brewer, DVM, MD, MS*

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**Dr. Brewer reports she receives grant/research support from the National Cancer Institute.**

SYNOPSIS: A recent study found that genotyping for human papillomavirus 16/18 is a reasonable approach to help calculate the risk of progression to CIN3 or worse.

SOURCE: Chatzistamatiou K, Moysiadis T, Moschaki V, et al. Comparison of cytology, HPV DNA testing and HPV 16/18 genotyping alone or combined targeting to the more balanced methodology for cervical cancer screening. *Gynecol Oncol* 2016;142:120-127.

First described by Georgios Papanikolaou in 1928 as a means to detect both uterine cancer and cervical cancer, the Pap smear was the standard of care until the liquid-based Pap smear (ThinPrep) was found to be more accurate.[1] Most institutions changed to this technology in 2003-2005. There have been multiple studies addressing how to best manage early detection for cervical cancer. The Pap smear is responsible for significantly reducing the incidence of invasive cervical cancer in the United States. However, widespread use has resulted in an enormous cost to society because of the false-positive rate of Pap smears as well as the false-negative rate. The role of human papillomavirus (HPV) in the etiology of cervical cancer was introduced in the 1960s by the German virologist Harold zur Hausen, who discovered HPV 11 and subsequently HPV 16 and 18. He discovered that these viral subtypes were strongly linked to cervical cancer and could be detected in 70% of cervical cancers. In 1999, further research revealed that 99.7% of cervical cancers are linked to HPV infections. HPV was not accepted as causative in cervical cancer until almost 2007.[2]

In this recent study from Greece, the authors evaluated multiple approaches to cervical cancer screening.[3] Women 25-55 years of age recruited for the HERMES (HEllenic Real life Multicentric cErvical Screening) study were screened in terms of cytology and high-risk (hr) HPV testing with HPV 16/18 genotyping. Women positive for cytology and/or hrHPV+ were referred for colposcopy, biopsy, and treatment. Ten screening algorithms based on different combinations of cytology, HPV testing, and HPV 16/18 genotyping were investigated for diagnostic accuracy. They balanced efficacy by calculating sensitivity, or the ability to detect all cases of CIN2 or greater vs. the rate of unnecessary colposcopies and the number of false positives. HPV testing alone had a sensitivity of 100% for CIN2 or greater but resulted in the largest number of colposcopies and a three-fold increase in false-positive rates compared to cytology alone. HPV testing with HPV 16/18 genotyping, referring HPV 16/18+ women directly to colposcopy, and hrHPV+ (non 16/18) women to reflex cytology (ASCUS threshold), as a triage method to colposcopy, reflects the best equilibrium between screening effectiveness and harm. HPV genotyping with reflex cytology for those patients who were hrHPV+ but 16/18-, and referral for colposcopy for those who were 16/18+, resulted in more colposcopies than the HPV with cytology triage but had a sensitivity of 83% compared to the HPV with cytology triage, which had a sensitivity of 53%. Each of the approaches either had excellent sensitivity but a high cost in terms of many more colposcopies or had poorer sensitivity but lower cost in terms of fewer colposcopies. The authors' approach was to balance risk of disease against harm caused by unnecessary testing.

Ultimately, the authors recommended that patients be hrHPV tested and, if positive, have genotyping done for HPV 16/18. Those who were HPV 16/18+ would be referred to colposcopy and those who were hrHPV+ but 16/18- would have cytology only performed. This approach was more cost effective and identified 83% of the women with CIN2 or greater.[4] HPV 16/18+ is responsible for 70% of cervical cancers and has a cumulative incidence of progressing to CIN3 over three years of 25-30%, while hrHPV+16/18- only has a cumulative incidence of progressing to CIN3 over three years of 5.4%, making this a reasonable approach.[5]

## ■ COMMENTARY

How can practitioners decide the best approach to screening for cervical neoplasia given the complicated algorithms and the confusing nature of so much seemingly contradictory data? We all have seen young women with high-grade dysplasia (≥ CIN2) who were followed every six months with repeat colposcopy and cytology for years and had multiple excisional procedures that probably were never going to progress to cancer. However, some women *will* progress to cancer a year or less after being diagnosed with high-grade cervical dysplasia if they are not treated. Genotyping for HPV 16/18 is a reasonable approach to help calculate the risk of progression to CIN3 or worse. Based on these data, as well as the results from the ATHENA trial, I now genotype any patient with an hrHPV type for HPV 16/18. If she is hrHPV+ 16/18- and cytology is negative, she

can have repeat evaluation in 12 months with cytology and HPV subtyping. Those patients who are HPV 16/18+ with negative cytology should have repeat colposcopy (± biopsy) and cytology in six months. Those who are cytology + (ASCUS or greater) need colposcopy and biopsy. Hopefully with a more thoughtful approach, we can do a better job of determining which women really need close screening and which women have a low risk of progression to cancer and, thus, can avoid the cost and morbidity associated with unnecessary treatment. ■


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ABSTRACT & COMMENTARY

# Glucose Screening: The Meaning of a Single Abnormal Value in a 3-hour Glucose Tolerance Test


***By John C. Hobbins, MD***

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



SYNOPSIS: A recent 25-study meta-analysis has shown that patients having only one elevation in a three-hour glucose tolerance test have similar maternal and fetal outcomes as patients diagnosed to have bona fide gestational diabetes.


SOURCE: Roeckner JT, Sanchez-Ramos L, Jijon-Knapp R, et al. Single abnormal value on three-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: A systematic review and meta-analysis. *Am J Obstet Gynecol* 2016;215:287-297.

Screening for diabetes has become complicated because methods in the literature vary according to different glucose challenges, glucose thresholds, and the timing for maternal blood sampling. The most common screening method in the United States has been to use a one-hour 50 g oral glucose load, followed by a blood sample taken one hour later. Published cutoffs vary between 130 and 140 mg/dL. (We use 140 mg/dL.) If the patient's blood sugar exceeds the selected value, it is recommended that she have a 100 g, three-hour glucose tolerance test (GTT). There are two sets of upper limits commonly used in the United States: the Coustan/Carpenter method and one fashioned by the National Diabetes Data Group (NDDG). Any patient having two or more levels above these preset thresholds would be labeled as having gestational diabetes (GD), while one abnormal or none would exclude the diagnosis.

What happens to the patient who flunks the one-hour screen but does not meet the "glucose tolerance cut" because she has only one value that exceeds the limit? Actually, in most cases she is considered to be a nondiabetic and less attention generally is paid to tracking her progress and outcome. Fortunately, an ambitious attempt has been made to do just that.

Roeckner et al scoured the literature from 1966 through 2015 to find studies involving patients who had abnormal one-hour glucose screens followed by a full 100 g GTT. They focused on studies that satisfied their maternal and neonatal outcome criteria. Then they compared outcomes from those with only one abnormal value with others who had two or more (GDs), as well as those "normals" who had no elevated values in their GTTs.

After applying seemingly rigorous exclusion criteria, the authors were left with 25 studies that had adequate outcome data on 4,466 women. When compared with those with no GTT elevations, the "one onlys" had higher rates of macrosomia (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.16-2.19), heavier mean birth weights by 44.5 g (95% CI, 8.10-80.8 g), higher rates of neonatal hypoglycemia (OR, 1.88; 95% CI, 1.05-3.38), total cesarean sections (OR, 1.69; 95% CI, 1.40-2.05), pregnancy-induced hypertension (OR, 1.55; 95% CI, 1.31-1.83), and low five-minute Apgar scores (OR, 6.10; 95% CI, 2.65-14.02). Increased rates in the same order also were found when the "one onlys" were compared with those with normal one-hour glucose screens and, therefore, never had a GTT. The clincher came when very similar rates of adverse outcome were found when the "one

onlys" were compared with true GDs, diagnosed by their having two or more abnormal values.

## ■ COMMENTARY

Anecdotally, I am sure the readers of *OB/GYN Clinical Alert* frequently have encountered patients who have flunked their one-hour screen and passed their three-hour GTTs, but still progress through pregnancy with all the fetal and maternal earmarks of a bona fide gestational diabetic. This study suggests that their outcomes are no different than "true" gestational diabetics.

It is granted that there are so many inconsistent diagnostic variables that confuse the issue, such as glucose levels used in the one-hour test, the size of the glucose load in the screening process, as well as the different diagnostic thresholds chosen in the three-hour diagnostic test. However, any patient who passes her GTT after an abnormal one-hour screen, but whose fetus has body-to-head disproportion, an estimated fetal weight of greater than 90th percentile, and a generous amount of amniotic fluid should raise our antennas to the point of suggesting:
1. Pursue a low glycemic (diabetic) diet,
2. Order another ultrasound scan after 34 weeks to assess fetal growth trajectory, and
3. Repeat at least the fasting and postprandial blood sugars after a month.

This information could become useful when these patients have reached 38 to 39 weeks, when macrosomia with body to head disproportion could affect labor and delivery management decisions. Also, any form of diabetes would put into question the benefit of any further time in utero for these patients and their babies. Last, these infants should be watched in the nursery for hypoglycemia.

This study suggests that patients in the intermediate glycemic category seem to have the same predilection for adverse neonatal outcomes as true gestational diabetics and, therefore, should not be ignored. ■

SPECIAL FEATURE

# Should We Still Be Performing Annual Pelvic Exams?


***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.**


The recent draft guidance from the United States Preventive Services Task Force (USPSTF) on the utility of periodic screening with the pelvic examination has inspired renewed debate on this topic.[1] The last time this subject made national news was in 2014 when the American College of Physicians (ACP) recommended against screening pelvic examinations in asymptomatic adult women.[2] At the time, I was not surprised that a group of internal medicine physicians recommended against routine pelvic examinations, as they typically are not very comfortable performing them. Nor do they have the anecdotal experiences that obstetrician-gynecologists share: the asymptomatic patients in whom we have diagnosed vulvar cancer, congenital anomalies, or pelvic masses with the pelvic exam. Surprisingly, the ACP document was endorsed by our colleagues in the American Academy of Family Physicians.[3] Based on national data, the USPSTF reported that the majority of preventive care visits to obstetrician-gynecologists (76%) included a pelvic examination compared to family medicine physicians (25%) and internal medicine physicians (14%).[1] The pelvic exam consists of three elements: 1) inspection of the external genitalia; 2) speculum examination of the vagina and cervix; and 3) bimanual palpation of the uterus, cervix, and adnexa. A rectovaginal exam also can be performed when indicated. Current American College of Obstetrician and Gynecologist (ACOG) guidelines endorse performing a pelvic examination annually in all patients 21 years of age or older, with the caveat that the decision to perform an internal exam should be a shared decision between the provider and the patient.[4]

## USPSTF CONCLUSIONS ABOUT PERIODIC SCREENING WITH THE PELVIC EXAMINATION

The recent publication from the USPSTF pertained to asymptomatic, non-pregnant women 18 years of age or older who are not at risk for specific gynecologic conditions.[1] The recommendations did not include using the pelvic exam for testing for cervical cancer or sexually transmitted infections. Overall, the USPSTF did not find any studies that assessed the effectiveness of pelvic examination in reducing all-cause mortality, reducing cancer- and disease-specific morbidity and mortality, or improving quality of life. The USPSTF noted that the pelvic exam, as an intervention, is difficult to study, as it can detect multiple gynecologic disorders including ovarian, uterine, vaginal, and cervical cancer, bacterial vaginosis, candidiasis, genital warts, genital herpes, trichomoniasis, pelvic inflammatory disease, cervical polyps, endometriosis, ovarian cysts, uterine fibroids, and pelvic organ prolapse. Nevertheless, the USPSTF reviewed the literature on the ability of the pelvic exam

to detect these various conditions and found only four studies on ovarian cancer (n = 26,432), two studies on bacterial vaginosis (n = 930), one study on genital herpes (n = 770), and one study on trichomoniasis (n = 150). The largest study on palpation of the ovaries to detect ovarian cancer, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial, determined that the sensitivity was only 2.8% (95% confidence interval, 0.6%-8.6%).[5] This is not new information for obstetrician-gynecologists, as we have long known that the bimanual exam is a poor test for ovarian cancer. Any abnormality on pelvic exam would be followed up with an ultrasound examination. Whether this leads to an increased use of healthcare resources than is otherwise needed is unknown. In the PLCO trial, the surgery rate after an abnormal ovarian palpation examination within one year of the abnormal screen was 11.2% (at the longest follow-up) with a complication rate (any complication: surgical, pulmonary, cardiovascular, infection, other) of 1.0%.[1] Potential false-positive or false-negative exams for infectious diseases are less concerning given that the vast majority of providers perform further tests for these conditions and do not rely on the pelvic exam alone. The USPSTF concluded that "the current evidence is insufficient to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic, non-pregnant adult women."

## ACOG'S RESPONSE TO THE USPSTF GUIDANCE

ACOG agreed with the USPSTF that more research is needed in this area and acknowledged that the ACOG recommendations for annual pelvic exams were based on expert opinion.[6] ACOG stated that women should have annual well-woman check-ups for preventive services and counseling whether or not a pelvic exam is included. ACOG also emphasized that a thorough review of systems should be performed, as some women may not recognize that certain signs or symptoms are abnormal. ACOG previously had stated that routine pelvic exams are not needed for the initiation of contraceptives (except intrauterine devices) and sexually transmitted infection testing (which can be done with urine samples or vaginal swab).[4] In addition, ACOG guidance previously had specified that it would be reasonable to stop performing pelvic examinations in asymptomatic women when a women's age or other health issues reach a point at which she would no longer choose to treat any conditions found on exam, presumably based on her life expectancy. ACOG's current recommendations for well woman care according to age groups can be found at: http://www.acog.org/About-ACOG/ACOG-Departments/Annual-Womens-Health-Care/Well-Woman-Recommendations.

## POTENTIAL PSYCHOLOGICAL HARMS OF THE PELVIC EXAM

The USPSTF was unable to find any studies that quantified the potential psychological harms of performing routine pelvic exams.[1] This was a big part of the ACP recommendation against routine pelvic exams. The ACP guidelines stated that, based on its review, a median of 35% of women across eight studies reported pain with pelvic exams and a median of 34% of women across seven studies reported fear, embarrassment, or anxiety with pelvic exams.[2] The concern is that these women would be less likely to return to a physician for further care. Of note, these studies were of low quality and were not included in the USPSTF review because of their lack of generalizability and applicability to the U.S. primary care setting. The USPSTF did acknowledge that certain subgroups of women, such as those with a history of sexual violence or abuse, chronic pelvic pain, or obesity, report more negative experiences from pelvic exams. Again, this is not new information for obstetrician-gynecologists, who I believe take great care to be compassionate and understanding when women present with these issues.

## TAKE-HOME MESSAGE

In a nationally representative survey of obstetrician-gynecologists, almost all surveyed physicians indicated that they would perform a bimanual examination during a routine visit with an asymptomatic patient.[7] Reasons cited as very important for performing the exam included adherence to standard medical practices (45%), patient reassurance (49%), detection of ovarian cancer (47%), and identification of benign uterine (59%) and ovarian conditions (54%). I agree with ACOG that the decision to perform an internal pelvic exam can be shared between the provider and patient. I believe that it has value, but I cannot say that it needs to be performed on an annual basis. I think the decision will come down to clinical judgment on the part of the provider based on the woman's individual circumstances. Nevertheless, I feel strongly that a routine external examination of the genitalia is important, given that many women do not perform self-examinations of that area and certainly other medical providers will not be looking "down there." I am also certain that obstetrician-gynecologists are the most trained in pelvic examinations and, therefore, are the best situated to make the exam as comfortable as possible for the patient. ■

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## CME/CE INSTRUCTIONS

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## CME/CE QUESTIONS

1. **Which of the following statements regarding findings of The Danish Sex Hormone Register Study of hormonal contraception and depression is true?**
   a. The risk of depression increased with the longest duration of use.
   b. The risk of depression was greatest in women younger than 20 years of age using combined oral contraceptives.
   c. The risk of depression decreased when pill users switched to the levonorgestrel intrauterine system.
   d. A sensitivity analysis that evaluated only first-time users of a contraceptive method supported the main results.

2. **HPV 16/18 are responsible for:**
   a. all cervical cancers.
   b. 70% of cervical cancers.
   c. 20% of cervical cancers.
   d. condyloma only.

3. **In the study by Roeckner et al, patients who had only one elevation in glucose levels in their glucose tolerance tests had higher rates of all but which of the following adverse outcomes, compared with those with no glucose elevations?**
   a. Neonatal hypoglycemia
   b. Macrosomia
   c. Cesarean section
   d. Cardiac anomalies
   e. Pregnancy-induced hypertension

## 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]

When to Start Progestin-only Contraceptives After Medical Abortion

OB/GYN
Clinical
Evidence-based commentaries
on women's reproductive health
[ALERT]

# 2016 Cumulative Index
## Volume 32, Number 9-12, Pages 65-96
## Volume 33, Number 1-8, Pages 1-64

**Please note, issue number is listed first followed by the page number**



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