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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

What Do the Urinary Microbiota and Incontinence Have to Do With Each Other?

By Chiara Ghetti, MD

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

SYNOPSIS: Increased diversity of the microbiota in women is associated with urgency urinary incontinence symptoms but not with stress urinary incontinence symptoms.

SOURCE: Thomas-White KJ, Kliethermes S, Rickey L, et al; National Institute of Diabetes and Digestive and Kidney Diseases Urinary Incontinence Treatment Network. Evaluation of the urinary microbiota of women with uncomplicated stress urinary incontinence. *Am J Obstet Gynecol* 2017;216:55.e1-55.e16.

The objective of this study was to investigate the relationships between urinary microbiota and characteristics of women undergoing surgery for stress urinary incontinence. Microbiota (or synonymously microbiome) refers to a community of microorganisms. In particular, Thomas-White et al investigated the female urinary microbiota, or in other words, the microbial communities that live in women's bladders. This was a sub-study of the Value of Urodynamic Evaluation study (VALUE), a National Institutes of Health-sponsored large, multicenter, clinical trial of women with uncomplicated stress urinary incontinence planning to undergo surgery.

Adult women were eligible for the VALUE study if they reported symptoms of stress urinary incontinence for three months with stress predominant urinary incontinence as measured by the Medical, Epidemiologic and Social Aspects of Aging (MESA) questionnaire subscale score, a post-void residual < 150 mL on examination, a negative urinalysis/standard urine culture, a positive provocative stress urinary test, and a desire for stress urinary incontinence surgery. Participants in the main study consented to contributing a single baseline urine specimen to a previously established biorepository of urine samples. Demographic and clinical variables (including stress

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and urgency urinary incontinence symptoms, menopausal status, and hormone use) were collected. The bacterial content of the urine was determined by sequencing the 16S ribosomal RNA gene.

Bacterial phylogenetic diversity and alpha diversity of urine samples were studied. Phylogenetic diversity refers to the evolutionary relationships between bacteria. This is described as a phylogenetic tree (a branching diagram that shows the evolutionary relationships between organisms). Alpha diversity refers to the measurement of diversity of a single sample, compared to beta diversity, which is the measurement between samples. The phylogenetic diversity and microbial alpha diversity were compared to subject demographics and urinary symptoms using generalized estimating equation models. Generalized estimating equations are a statistical methodology used to analyze correlated data (data where mutual relationships exist).

Samples from 197 of the 630 VALUE study participants were used in this analysis. Demographic and clinical characteristics of the 197 participants were similar to those of the overall trial population. The majority of samples (174) had been obtained by clean catch, with the remaining by catheterization. The majority of participants were non-Hispanic Caucasians. Forty-two percent were premenopausal, 31% postmenopausal without current exogenous hormone use, and 18% were using exogenous hormones.

Subjects reported stress predominant symptoms consistent with study eligibility, and many had concomitant urinary symptoms. The majority of urine samples (86%) had detectable bacterial DNA. Bacterial diversity was significantly associated with higher body mass index (BMI), increased urgency symptoms as measured by the MESA urge index score, and hormonal status. Hormone-positive women (premenopausal and those currently on exogenous estrogen) have predominant bacteria with a higher prevalence of *Lactobacillus* or *Gardnerella* types (66%) compared to hormone-negative women. Hormone-negative women (postmenopausal not on exogenous hormones) have a higher bacterial diversity with greater number of nondominant bacteria, which is associated with a lower frequency of *Lactobacillus* or *Gardnerella* urotypes (38%) compared to estrogen-positive women. No associations were found between bacterial diversity and stress urinary incontinence symptoms.

■ COMMENTARY

The findings reported in this study show that women undergoing stress urinary incontinence surgery have measurable urinary microbiota. The analysis suggests that increased urinary bacterial diversity is associated with urgency urinary incontinence symptoms, hormonal status, and increased body mass index and not associated with stress urinary incontinence symptoms.

Studies have shown that in a healthy human body, microbial cells outnumber human cells by 10 to one. This microbiome is thought to be an integral component in the maintaining health and proper function of the immune system.[1] Until recently, the community of microbes with which we coexist largely was unstudied. In 2008, the NIH began funding the Human Microbiome Project to help identify and characterize the microorganisms associated with humans and their role in health and disease.[2] To date, studies have focused mainly on the gut, vagina, oral cavity, and skin. New data recently have been published, reporting a large number of bacterial genomes from different body sites.[3]

Very little is still known about the urinary microbiome. In fact, before the last decade, many of us were taught that urine was sterile. The current study and several other prior studies by the authors have demonstrated by DNA analysis and microbial culture that even when urine cultures are negative, detectable bacterial communities containing mixtures of urinary and genital tract bacteria exist in the urine of some adult women.[4,5] Studies of urine from women with lower urinary tract symptoms demonstrate that large numbers of bacteria are present, often undetected by routine cultures.[6]

This study has a number of strengths, including the multicenter nature of the study, extensive characterization of participants, as well as the use of cutting-edge sequencing techniques and state-of-the art analytic approaches. Future studies will benefit from using controls matching for the significant associations found (BMI, hormone status, and lower urinary tract symptoms) and from the addition of vaginal and/or rectal samples to inform how these nearby microbiomes may affect the bladder.

The current study further highlights the diversity of the urinary microbiomes and the likely associations among microbiome characteristics, BMI and hormone status, and urinary symptoms. In particular, urinary urgency symptoms may be associated with increased bacterial diversity in the absence of a predominant bacterial type. A 2008 Cochrane review examining the use of vaginal estrogen in the treatment of women with recurrent urinary tract infections (UTIs) concluded that vaginal estrogens are effective in reducing the number of UTIs in postmenopausal women with recurrent UTIs.[7] The current study helps bring to light a significant relationship between hormone status and urinary microbiome that may explain these findings. We are just at the beginning of an exciting new understanding of the urinary microbiome and its effect on the care of women with urinary urgency symptoms and with recurrent UTIs. ■

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ABSTRACT & COMMENTARY

Dating Pregnancy: What Is the Most Accurate Method?

By John C. Hobbins, MD

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

SYNOPSIS: The NICHD Fetal Growth Studies – Singletons investigation recently yielded a new formula for determining gestational age based on standard biometric information. When compared to an often-used formula, it appeared to be more accurate after 21 weeks of gestation.

SOURCE: Skupski DW, Owen J, Kim S, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Developmental Fetal Growth Studies. Estimating gestational age from ultrasound fetal biometrics. *Obstet Gynecol* 2017;130:433-441.

When dating pregnancies, the clinician deals with two sources of information: patient history and ultrasound findings. The latter is certainly the most objective source, but there are inherent machine- and human-related drawbacks that affect the accuracy of these ultrasound dating methods.

Since equipment and user expertise have improved over the years, Skupski et al, using data generated under the support of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), recently pitted a newly constructed formula for gestational age (the NICHD gestational age formula) against a formula published in 1984 (the Hadlock formula),[1] which the authors described as "being in common use today." Both formulas use the same biometric variables: head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL).

The study involved 803 non-Hispanic black (28.6%), 781 Hispanic (27.9%), 751 non-Hispanic white (27.9%), and 467 Asian (16.7%) women. All women in the study had regular periods and first trimester ultrasound exams in which the crown rump lengths (CRLs) were within five days of the last menstrual period at 8/0 to 10/6 weeks, six days between 11/0 and 12/6 weeks, and seven days at 13/0 and 13/6. The menstrual dates were then considered as the true gestational age. The patients were followed with serial ultrasound exams through the second and third trimesters. Data from half of these patients were used to construct a gestational age equation, which then was applied to the other half of the study population. The idea was to see how close to the true gestational (menstrual) age the new formula performed, compared with the Hadlock formula. Since the splay in biological variation widens as pregnancy progresses, three gestational age windows were chosen for analysis: 14 to 20 weeks, 21 to 27 weeks, and 28 to 40 weeks. The authors also compared the performance of the new formula in each ethnic group and across various body mass indices (BMIs).

The NICHD formula performed no better than the Hadlock formula between 14 to 20 weeks (± 7 days).

However, it was a little better at 21 to 27 weeks (± 10 days), with an average "estimation error" (EE) of 10.4 vs. 11.2 days. At 28 to 40 weeks (± 17 days), the EE was 17.0 vs. 19.8 days. It should be noted that after 34 weeks, the Hadlock formula was highly inaccurate. Interestingly, there were no statistical differences in accuracy between ethnic or BMI groups with either formula.

■ COMMENTARY

The authors made the point that more accurate dating will reduce the amount of unnecessary interventions for post-maturity and will enable clinicians to better identify true prematurity. However, it also must be noted that the diagnosis of two of the most vexing problems, fetal growth restriction and macrosomia, also depend on gestational age. So, anything we can do to get it right will help.

With the introduction of early screening with nuchal translucency (NT) and the growing desire for patients to have the earliest information available, first-trimester scans are being performed much more frequently, yielding CRL measurements that should trump any later biometric formula for gestational age. Skupski et al found that during the second window of opportunity (14 to 21 weeks), when many patients now have fetal anatomy scans, the new NICHD formula would provide little benefit over other commonly used formulas. Even the one- to two-day advantage of the new formula is of questionable benefit at 21 to 28 days. However, the new formula could make a difference in those showing up for their first scan after 28 weeks, when there would be about a week's worth of advantage in accuracy over the Hadlock formula. The study data suggest that the Hadlock formula is virtually worthless after 34 weeks.

The nuances regarding ultrasound functions and formulas can be confusing. The new NICHD formula only deals with gestational age. With most ultrasound machines, users can choose their favorite formula or the formula, usually the Hadlock formula, loaded by the ultrasound manufacturer. The displayed result is labeled as the composite ultrasound age (CUA). In addition, the machine will automatically average all the biometric measurements (AC, BPD, FL, and HC), labeling the result as the arithmetic ultrasound age (AUA). In 1984, Hadlock et al compared their CUA formula with the AUA and found no significant differences between the two.[1] This has not been done with the new NICHD formula, but the CUA is likely to be very similar to the AUA.

The plot thickens when one attempts to determine the fetal size. There are more than 50 formulas to calculate fetal weight, using two to five biometric measurements. For example, the Hadlock formula for estimation of fetal weight (EFW) employs the HC, BPD, AC, and FL.[2] Not surprisingly, this is the one most often used.

The third step is to determine how a given fetus's size matches up to what is expected, based on its assigned gestational age. This is done by plotting the EFW into a nomogram that best fits the population studied. Often, the user simply will apply the machine's default nomogram (you guessed it, the Hadlock formula),[2] which was constructed from 392 Caucasian patients at sea level (Texas). This enables the EFW to be displayed as a percentile. This is the step that lends itself most to a customized approach, since this Texas cohort cannot be expected to be identical to, for example, a mixed ethnic population at 5,000 feet above sea level. To adjust for this, Gardosi et al developed the concept of a customized standard for each fetus.[3] This and other formulas have been based on an individual patient's historical factors, physique, ethnic background, parity, habits, etc. Tailor-made formulas tend to have a greater sensitivity for weight extremes and even have correlated better with perinatal mortality and morbidity in intrauterine growth restriction (IUGR) fetuses.[4]

Through the years, software engineers and researchers have attempted to make life better for clinicians by adding various new wrinkles in technology and algorithm formulations. While some of these endeavors have been helpful, others may have just confused some of the tasks at hand. Fine-tuning true gestational age certainly is worth tackling, but up until about 28 weeks, the benefit of the NICHD formula over existing formulas is underwhelming and represents the least important of the three steps. The last step is the most important regarding identifying small for gestational age and large for gestational age fetuses, but this devil's advocate could point out that the customized formulas for EFW, while correlating best with some neonatal outcomes and diminishing false-positive results, may be missing deprived late IUGR fetuses with borderline EFWs who might develop neurological problems in childhood.[5] Since these fetuses could be identified only by middle cerebral artery analysis alone, a case certainly could be made for casting a wider net with a more inclusive formula. ■

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ABSTRACT & COMMENTARY

Should Endocervical Curettage Be Performed Routinely During Colposcopy?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, and has served as a consultant for Bayer and Pharmanest.

SYNOPSIS: In this study, routine endocervical curettage (ECC) among women age 30 and older detected CIN 2 or worse in 14.4% of cases with higher likelihood of detection among women with high-grade squamous intraepithelial lesion, ASC-H, positive HPV 16 infection, or high grade colposcopic impression. The additional yield of ECC over lesion-directed ectocervical biopsies decreased with each additional biopsy.

SOURCE: Liu AH, Walker J, Gage JC, et al. Diagnosis of cervical precancers by endocervical curettage at colposcopy of women with abnormal cervical cytology. *Obstet Gynecol* 2017; Nov 3. doi: 10.1097/AOG.0000000000002330. [Epub ahead of print].

This is a secondary analysis of the Biopsy Study, a cross-sectional study from the University of Oklahoma Health Science Center that evaluated the incremental benefit of multiple biopsies at colposcopy. Women were excluded from the study if they had previous treatment of cervical dysplasia, prior chemotherapy or radiation for cervical neoplasia, pregnancy, or known HIV infection. According to study protocol, up to four cervical biopsies were taken of acetowhite lesions. When less than four biopsies were taken, an additional non-directed biopsy was taken of a normal-appearing area on the transformation zone of the cervix. Women age 30 years or older were supposed to routinely receive endocervical curettage (ECC) and women younger than 30 years of age received ECC for the following: discrepancy between colposcopic findings and high-grade squamous intraepithelial lesion (HSIL) referral cytology, unsatisfactory examination, or atypical glandular cells (AGC) or adenocarcinoma in situ (AIS) cytology. A sharp Kevorkian curette was used to assess the endocervix, except in women with severe cervical stenosis, in whom a Cytobrush was permitted. Biopsy results were categorized as low-grade squamous intraepithelial lesion-LSIL (CIN [cervical intraepithelial neoplasia] 1 or less, p16 negative-CIN 2) or high-grade intraepithelial lesion-HSIL (p16 positive-CIN 2, CIN 3, cancer). The authors evaluated the yield of ECC in identifying CIN 2 or worse by itself and the additional yield of ECC in identifying CIN 2 or worse not otherwise found on biopsies of ectocervical lesions.

Of 204 women aged 30 years and older, 181 (89%) received an ECC. Among women younger than 30 years of age, 100 of 477 (21%) underwent an ECC. The ECC found CIN 2 or worse among 26 of the 181 women age 30 and older (14.4%). The yield of ECC in detecting CIN 2 or worse increased with age, from 10.1% among women 20 to 29 years of age to 25% among women 60 to 69 years of age. Yield was higher in women with ASC-H (atypical squamous cells, cannot rule out high grade) or HSIL or worse (includes AGS, AIS, squamous cell carcinoma) cervical cytology compared to women with ASCUS (atypical squamous cells of undetermined significance) or LSIL (low-grade squamous intraepithelial lesion) cytology (27.1% vs. 7.3%; $P < 0.05$). Yield also was higher in women positive for HPV 16 infection (24.4% vs. 11.5%; $P < 0.05$) or a high-grade colposcopic impression (26.8% vs. 8.0%; $P < 0.05$). The authors stratified women based on indications for ECC according to the current U.S. management guidelines for cervical cancer screening and management[1]: for ASCUS or LSIL cytology, ECC is preferred when no lesions are found or exam is unsatisfactory, and it is acceptable when exam is satisfactory with visible colposcopic lesions; for ASC-H or HSIL, ECC is preferred for all nonpregnant women. Among women with ASCUS or LSIL, ECC found CIN 2 or worse in 4.3% of normal exams, 13% of unsatisfactory exams, and 1.9% of satisfactory exams with positive findings on the ectocervix. Among women with ASC-H or HSIL, ECC found CIN 2 or worse in 26% of cases. The additional yield of ECC for detecting precancers otherwise missed by ectocervical biopsies was 14.4% when no lesion-directed ectocervical biopsies were taken but decreased to 7.7%, 5.0%, 4.4%, and 3.9% when one, two, three, and four lesion-directed ectocervical biopsies were performed, respectively.

■ COMMENTARY

The study authors previously showed that increasing the number of ectocervical biopsies increased precancer detection during colposcopy.[2] The Biopsy Study showed a 25% increase in detection between the first and second lesion-directed biopsy and a 10% increase between the second and third lesion-directed biopsy. Although it is acknowledged that ECC is useful in older women in whom the transformation zone is receding into the endocervix as a result of hormonal changes, the question of whether to add ECC to colposcopy procedures routinely has been debated. Current American Society

for Colposcopy and Cervical Pathology (ASCCP) guidelines prefer ECC be performed for any high-grade cytology and in women with ASCUS or LSIL cytology whose exams are unsatisfactory or in whom no lesions are found.[1] The current study seems to support these recommendations. The authors also believed that HPV 16 also indicated the need for ECC, especially in older women. In current clinical practice, however, the subtype of high-risk HPV is not always known at the time of colposcopy. The lack of selection bias as to who received ECC among women age 30 years and older is a major strength of this study. However, there are some limitations to this study, including smaller numbers of older women and low prevalence of HPV 18 infection, which limited analysis in some strata.

The ASCCP recently released consensus guidelines that outline recommendations for colposcopy standards across the United States where a wide range of provider types perform colposcopy.[3] To date, colposcopic practice has been based on how one was trained, and there were no national guidelines specifically outlining pre-colposcopy evaluation, terminology, documentation, or the number of biopsies recommended. The ASCCP convened an expert committee and performed systematic analyses of the evidence to generate the recommendations. For example, the ASCCP recommended the minimum criteria for reporting findings at colposcopic examination include: squamo-columnar junction visibility (full visualized/not fully visualized), acetowhitening (yes/no), lesion(s) present (acetowhite or other) (yes/no), and colposcopic impression (normal/benign, low grade, high grade, cancer). Comprehensive documentation would add the following: cervix visibility (fully visualized/not fully visualized), lesion visualized (fully visualized/not fully visualized), location of lesion(s), size of lesion(s), vascular changes, and other features of lesion(s) (color, contour, borders, Lugol's uptake, etc.). The executive summary of the recommendations are listed below.[3]

1. Adapting colposcopy practice to previous risk and colposcopy impression
Recommendation: Colposcopy practice may be modified based on the risk level (which can be viewed as the probability of finding precancer/cancer at the time of the procedure), based on reason for referral and colposcopy impression.

2. Number and type of biopsies taken at colposcopy
Recommendation: Multiple biopsies targeting all areas with acetowhitening, metaplasia, or higher abnormalities are recommended. Usually, at least two and up to four targeted biopsies from distinct acetowhite lesions should be taken.

3. Biopsy practice in women with low risk of precancer
Recommendation: Nontargeted biopsies are not recommended for women referred to colposcopy at the lowest end of risk, i.e., those with less than high-grade squamous intraepithelial lesion cytology, no evidence for HPV 16/18, and a completely normal colposcopic impression (i.e., no acetowhitening, metaplasia, or other visible abnormality).

4. Biopsy practice in women with very high risk of precancer
Recommendation: In nonpregnant women 25 years and older with very high risk of precancer (at least two of the following: high-grade squamous intraepithelial lesion cytology, HPV 16 and/or HPV 18 positive, high-grade colposcopy impression) either immediate excisional treatment without biopsy confirmation, or colposcopy with multiple targeted biopsies is acceptable. Endocervical sampling should be conducted according to the 2012 ASCCP Management Guidelines. If biopsies are taken and do not show precancer, management according to the 2012 ASCCP Management Guidelines is recommended.

These guidelines will help with colposcopy training, ensuring universal practice standards and quality improvement activities. ■

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ABSTRACT & COMMENTARY

Does Postpartum Use of Hormonal Contraception Increase Risk of Depression?

By Jeffrey T. Jensen, MD, MPH, Editor

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Dr. Jensen reports that he is a consultant for and receives grant/research support from Bayer, Abbvie, ContraMed, and Merck; receives grant/research support from Medicines 360, Agile, and Teva; and is a consultant for MicroChips and Evofem.

SYNOPSIS: An analysis of a large insurance database showed no consistent effect between postpartum initiation of hormonal contraception and the subsequent diagnosis of depression.

SOURCE: Roberts TA, Hansen S. Association of hormonal contraception with depression in the postpartum period. *Contraception* 2017;96:446-452.

Prior research has suggested an association between hormonal contraception initiation and depression. Roberts and Hansen sought to determine if starting hormonal contraption in the postpartum interval would influence the risk of depression diagnosis or treatment during the first year following birth. They used the Military Health System Management Analysis and Reporting Tool (M2) to perform a secondary analysis of insurance records from 75,528 postpartum women enrolled in the U.S. military medical system, who delivered between October 2012 and September 2014. The analysis excluded women with a prior history of depression or use of antidepressants in the two years prior to delivery. The M2 contains medical and pharmacy billing records of all individuals who used TRICARE Prime (active duty and retired service members and family members younger than 26 years of age) and includes enrollment status for each month. The database includes information from both military and civilian treatment facilities including electronic medical record and billing statements.

Using these records, the authors identified subjects with a diagnosis of major depression or antidepressant medication prescriptions during the 12 months after delivery (the primary outcome). They assessed the relationship between hormonal contraception use with subsequent antidepressant use or diagnosis with depression in the first 12 months postpartum using Cox proportional hazards regression, with a time-dependent covariate measuring exposure to hormonal contraception. Key demographic variables included age, insurance eligibility status, and the insurance sponsor's rank (a proxy for socioeconomic status).

The average age at delivery was 28.5 years, most of the women had a senior enlisted sponsor (52.9%) and were family members of active duty service members (74.4%), and the average follow-up period after delivery was 8.9 months. Overall, 7.8% of postpartum women received a prescription for an antidepressant, and 5.0% received a diagnosis of depression. Both antidepressant use and depression diagnosis were associated with younger age, lower socioeconomic status, and a history of military service. Fewer than half of the women (41.7%) initiated hormonal contraception in the 12 months after delivery. The majority (63%) used the norethindrone-only pill. Other contraception choices included the levonorgestrel intrauterine systems (LNG-IUS) (9.8%), etonogestrel implant (8.7%), combined pills (13.9%), and the ethinyl estradiol/etonogestrel vaginal ring (CVR) (4.5%). Women started the norethindrone pill earlier than other methods, while those using long-acting reversible contraception methods contributed more time to follow-up.

Compared to women with no hormonal contraceptive use, use of etonogestrel-containing contraception was associated with a higher risk of antidepressant use (implant: adjusted hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.06-1.41; CVR: HR, 1.45; 95% CI, 1.16-1.80). In contrast, use of norethindrone-only pills was associated with a lower risk of antidepressant use (HR, 0.58; 95% CI, 0.52-0.64) and depression diagnosis (HR, 0.56; 95% CI, 0.49-0.64), and use of the LNG-IUS was associated with a lower risk of depression diagnoses (HR, 0.65; 95% CI, 0.52-0.82). None of the other contraceptive methods showed statistically significant relationships.

The authors concluded that the risk of major depression diagnosis and antidepressant use in the postpartum period varies with the type of hormonal contraception used.

■ COMMENTARY

Last year, I highlighted the Danish National database study of Skovlund et al, who reported an association between initiation of hormonal contraception and first diagnosis of depression.[1] This new study by Roberts and Hansen uses a U.S. Military Insurance Database to ask a similar question, focusing on contraception initiation in the postpartum interval. Databases offer substantial strengths for epidemiologic study, in particular the linkage of prescription data to clinical outcomes and large subject numbers that yield precise estimates of risk with tight confidence intervals. However, bias must be considered as an explanation of any epidemiologic finding. These include the absence of baseline information concerning important confounders, and the inability to control for prescription bias and the healthy user effect. Readers must keep in mind that database studies are not randomized, controlled trials. Database studies do not have the resolution to exclude chance as the explanation for weak associations, risk estimates < 2.0 (or > 0.5).[2]

Skovlund et al showed weak but consistent associations for a variety of hormonal methods including combined pills, the patch, and the ring, and also with progestin-only methods such as pills, implants, and the LNG-IUS. Although the Roberts and Hansen paper showed

a similar magnitude of increase in the risk of depression associated with use of the etonogestrel implant and ring, a protective effect was seen with both the LNG-IUS and the norethindrone progestin-only pill, and no association with other combined pills. While many women accept a prescription for progestin-only pills and never take them, it is hard to understand why this could result in protection from depression. It requires less imagination to think that women who initiate a more effective method like the implant might be under early pressure to initiate sexual activity. Adjusted risks estimates exceeded 2.0 with teen birth (adjusted HR, 2.03; 95% CI, 1.50-2.76) and low socioeconomic status (e.g., junior enlisted sponsor) (adjusted HR, 2.09; 95% CI, 1.67-2.63). The social context that influences contraception choice also may influence depression risk. In the military, nonuse of contraception may be associated with deployment of a loved one.

Although this study has many flaws, I find the absence of any consistent effect with respect to depression risk and initiation of a progestin-only or combined hormonal method of contraception reassuring. Full evaluation of this question will require well-designed, large, prospective studies that fully control for potential baseline confounders. Perhaps European regulatory authorities will require such a study in the future. Until we have better information, clinicians should continue to openly discuss the risks and benefits of hormonal methods and encourage patients to report symptoms of mood changes. As I have mentioned previously, 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. ■

REFERENCES

1. Skovlund CW, Morch LS, Kessing LV, Lidegaard O. Association of hormonal contraception with depression. *JAMA Psychiatry* 2016;73:1154-1162.
2. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-252.

CME/CE QUESTIONS

1. **The study by Thomas-White et al indicates that the urinary microbiome:**
   a. does not exist and that urine is sterile.
   b. has no predominant bacterial type.
   c. is likely independent of hormone status.
   d. is associated with urinary urgency incontinence.
2. **Which of the following best describes the greatest benefit of the new NICHD dating formula?**
   a. Between 18 and 21 weeks
   b. Between 21 and 27 weeks
   c. Between 28 and 40 weeks
   d. It is of equal benefit in all trimesters.
3. **Customized formulas for estimated fetal weight correlated better with immediate neonatal outcome than population-based standard formulas.**
   a. True
   b. False
4. **In the study by Liu et al, detection of CIN 2 or worse by ECC was more likely in all of the following scenarios *except*:**
   a. high-grade colposcopic impression.
   b. high-grade referring cytology.
   c. HPV-18 infection.
   d. older women.
5. **Among postpartum women in the Military Insurance Database, the risk of depression diagnosis was increased with which of the following?**
   a. Teen birth and low socioeconomic status
   b. Use of combined oral contraceptives
   c. Use of the LNG-IUS
   d. Use of the norethindrone progestin-only pill

[IN FUTURE ISSUES]

The Debate Continues on Salpingectomy