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OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Baby-Friendly Policies May Be Ineffective in Improving Breastfeeding Outcomes in the United States

By Nicole Cirino, MD, CST, IF

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

SYNOPSIS: Data analysis from the 2018 Centers for Disease Control and Prevention Breastfeeding Report Card failed to show improvements in breastfeeding outcomes in Baby-Friendly facilities over statewide breastfeeding initiation programs.

SOURCE: Bass JL, Gartley T, Kleinman R. Outcomes from the Centers for Disease Control and Prevention 2018 Breastfeeding Report Card: Public policy implications. *J Pediatr* 2019; Oct. 10. [Online ahead of print].

The Baby-Friendly Hospital Initiative (BFHI) is a global program launched in 1991 by the World Health Organization (WHO) and the United Nations Children's Fund with the aim to improve breastfeeding rates. To receive a Baby-Friendly designation, hospitals must implement the Ten Steps to Successful Breastfeeding and comply with the International Code of Marketing of Breast-Milk Substitutes. In 2019, 28% of births occurred in the more than 600 Baby-Friendly designated facilities in the United States. The 10 steps include, among other things: breastfeeding within an hour of birth, giving healthy infants no drink other than breast milk (i.e., no formula), eliminating pacifiers and bottles, and practicing rooming-in to "allow mothers and infants to remain together 24 hours a day."[1] The guidelines were revised in 2018 "to respect maternal autonomy and avoid judgmental attitudes which could infringe on the mother's dignity."[2]

The primary objective of this study was to compare states with high penetrance of Baby-Friendly designated facilities to states with low penetrance

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This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

of Baby-Friendly designated facilities in terms of targeted breastfeeding outcomes. Specifically, the researchers looked at the effect of the Baby-Friendly designation on in-hospital breastfeeding initiation, as well as breastfeeding outcomes at three, six, and 12 months post-discharge.

The authors analyzed data from the 2018 Centers for Disease Control and Prevention (CDC) Breastfeeding Report Card referencing breastfeeding parameters in the 2015 birth cohort. The CDC annual Breastfeeding Report Card provides state-specific data on breastfeeding outcomes after discharge and includes WHO Baby-Friendly Hospital Initiative (BFHI) designation rates by state. These data rely on maternal recall when the children are between 19 and 35 months of age. Data collected included initiation percentages (low to high), any breastfeeding at six and 12 months, and exclusive breastfeeding at three and six months. Linear regression models were used to determine the strength of the association of breastfeeding initiation and Baby-Friendly penetrance and attainment of post-discharge breastfeeding rates. All hospital births from 50 states, three territories, and the District of Columbia were included in the study.

As expected, breastfeeding initiation, in itself, was significantly associated with all breastfeeding outcomes ($P < 0.0001$), including any breastfeeding at six and 12 months and exclusive breastfeeding at three and six months. This was the case in states with both high and low penetrance of Baby-Friendly facilities.

However, Baby-Friendly designated facilities did not demonstrate a significant association with any post-discharge breastfeeding outcomes over statewide programs. (Any breastfeeding at six or 12 months, $P = 0.36$ vs. exclusive breastfeeding through three or six months, $P = 0.256$). Further, there was no association between Baby-Friendly designation and breastfeeding initiation rates ($P = 0.67$).

The authors concluded that states with substantially fewer births at Baby-Friendly facilities, and that have high breastfeeding initiation rates, have had greater success in promoting breastfeeding after discharge. The researchers concluded that breastfeeding initiation is a more important outcome than breastfeeding exclusivity during the birth hospitalization. In summary, states with high Baby-Friendly designation penetrance did not demonstrate any positive post-discharge breastfeeding association.

Limitations to the study come from the data set itself. The Breastfeeding Report Card relies on maternal recall, was conducted by cell phone, and did not gather key demographic data such as race, ethnicity, poverty, and educational level.

■ COMMENTARY

With a global initiative backed by WHO and a name as benign as "Baby-Friendly," many early opponents with concerns had little success in pushing back against the adoption of the BFHI movement. Many of us in the women's

[Baby-Friendly designated facilities did not demonstrate a significant association with any post-discharge breastfeeding outcomes over statewide programs.]

mental health community have been particularly concerned with overly rigid enforcement of the 10 steps. We are routinely advocating for taking into consideration the mental health of the mother in the universal enforcement of such a policy.[3]

These guidelines do not have modifications in place for women with moderate or severe mental illness, acute postpartum hemorrhage or other perinatal complications, concurrent use of pain medication, or, until recently, a woman's personal preference. Many facilities no longer have special care nurseries available, so in-hospital rooming-in is the standard expectation.

Sleep preservation in the first three weeks postpartum is one of the key strategies for prevention of severe postpartum

episodes, and sleep deprivation has been implicated in the onset of severe postpartum psychiatric pathology.[4] This high-risk period occurs during the same time period that the BFHI advocates for 24-hour-a-day "rooming together" and "giving infant no drink other than breast milk."

The authors of this article are pediatricians who have published previously about their criticism of the BFHI.[5] They cite recent concerns that the BFHI may increase adverse neonatal sentinel events, including suffocation injuries like sudden unexpected postnatal collapse (SUPC), newborn falls, and newborn dehydration and jaundice. SUPC occurs in otherwise-healthy term newborns, usually in the first 24 hours of life, and frequently is caused by the mother falling asleep during or after breastfeeding.[6] This report raised the important question of whether bed-sharing, a practice that is discouraged at home, can be done safely in the hospital without medical supervision.[7]

This is the first evidence to date that shows a limitation in the effectiveness of the primary goal of the BFHI. These data alone do not prove that BFHI overall creates more risk than benefit to the mother-infant dyad. However, the fact that this "one-size-fits-all" initiative may not actually increase rates of breastfeeding in the general U.S. population, and may even hinder rates, should inform our in-hospital birthing practice moving forward. ■

REFERENCES

1. Baby-Friendly USA. The ten steps to successful breastfeeding. Available at: https://www.babyfriendlyusa.org/for-facilities/practice-guidelines/10-steps-and-international-code/. Accessed Jan. 16, 2020.
2. World Health Organization. Ten steps to successful breastfeeding (revised 2018). Available at: https://www.who.int/nutrition/bfhi/ten-steps/en/. Accessed Jan. 16, 2020.
3. MGH Center for Women's Mental Health, Nonacs R. Does Baby-Friendly have to be mom-unfriendly? June 12, 2017. Available at: https://womensmentalhealth.org/posts/baby-friendly-mom-unfriendly/. Accessed Jan. 16, 2020.
4. Lewis KJS, Di Florio A, Forty L, et al. Mania triggered by sleep loss and risk of postpartum psychosis in women with bipolar disorder. *J Affect Disord* 2018;225:624-629.
5. Bass JL, Gartley T, Kleinman R. Unintended consequences of current breastfeeding initiatives. *JAMA Pediatr* 2016;170:923-924.
6. Gomez-Pomar E, Blubaugh R. The Baby Friendly Hospital Initiative and the ten steps for successful breastfeeding. A critical review of the literature. *J Perinatol* 2018;38:623-632.
7. Steinhorn RH. Breastfeeding, Baby-Friendly, and safety: Getting the balance right. *J Pediatr* 2019; Dec. 3. [Online ahead of print].

ABSTRACT & COMMENTARY

Knowledge of Pelvic Floor Disorders Among Pregnant and Postpartum Women

By Chiara Ghetti, MD

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

SYNOPSIS: Pregnant and postpartum patients lack knowledge about urinary incontinence and prolapse.

SOURCE: Mckay ER, Lundsberg LS, Miller DT, et al. Knowledge of pelvic floor disorders in obstetrics. *Female Pelvic Med Reconstr Surg* 2019;25:419-425.

The objective of this study was to examine knowledge regarding pelvic disorders, in particular urinary incontinence (UI) and pelvic organ prolapse (POP), among pregnant and postpartum women and to identify the characteristics of subjects who lack knowledge about UI and POP.

This is a cross-sectional, multicenter study of women presenting for prenatal or post-natal care. Subjects were recruited from nine locations with affiliations to three hospitals in Connecticut and were included if they were 18 years of age or older and either pregnant or up to eight weeks postpartum. Women were asked to complete a self-administered survey containing study measures and were excluded if they had completed the survey previously. The primary outcome measure was pelvic floor disorder (PFD) knowledge, which was assessed using the Prolapse and Incontinence Knowledge Questionnaire (PIKQ). This is a 24-item, validated, self-administered questionnaire comprised of two independently scored 12-item subscales. It assesses women's knowledge about UI and POP, respectively, in the areas of disorder etiology, epidemiology, diagnosis, and treatment. Subjects also completed sociodemographic information and the Pelvic Floor

Distress Inventory-20 questionnaire assessing PFD symptoms. The primary outcomes were the percentage of women with a lack of knowledge proficiency, defined as correctly responding to 80% and 50% of the PIKQ UI and POP subscales, respectively. Associations between lack of knowledge and demographic characteristics were explored with univariate and multivariable analyses.

Three hundred ninety-nine subjects completed some portion of the study questionnaires, with 376 and 364 participants completing the UI and POP subscales, respectively. The mean participant age was 28.5 ± 6.0 years. Two-thirds of participants were unmarried (61%) and had delivered at least one child (67%). One-third of women self-identified as white, non-Hispanic (33%). The majority of subjects were pregnant (93.2%) and nearly two-thirds were in the third trimester 64.6% (n = 248). Overall, 39% (n = 151) reported incontinence symptoms, while 4.8% (n = 18) reported seeing or feeling a vaginal bulge. The majority of women showed a lack of knowledge proficiency about UI (74%) and POP (70%). In multivariable analyses, the authors reported that patient characteristics significantly associated with a lack of knowledge proficiency regarding UI include Hispanic race, primiparity, and lower levels of education. For POP, lower level of education was a characteristic significantly associated with lack of knowledge proficiency, while women reporting prior visits to a urologist or urogynecologist and women working in a medical field were more likely to have a higher knowledge proficiency.

[Patient knowledge is a barrier to early care, alongside a lack of routine screening by primary care physicians.]

■ COMMENTARY

Overall, women have poor knowledge regarding PFDs. A prior study by the authors demonstrated that community-dwelling women with a mean age of 49 years (range 19-80+) lacked knowledge proficiency in both UI and POP.[1] Seventy-one percent of women lacked UI knowledge and 48% lacked POP knowledge. Chen et al, using the same questionnaire (PIKQ), found a lack of knowledge among women seeking primary care.[2,3] In the cohort, 72% lacked knowledge about UI and 54% lacked POP knowledge. The current study finds a persistent lack of knowledge in pregnant and postpartum women; 74% of women lacked UI knowledge and 70% lacked POP knowledge.

Lack of knowledge has been found to be associated with educational status and also with a lack of awareness that PFDs are a medical condition. Mandimika et al found significant racial disparities in pelvic floor knowledge.[4] In that study of community-dwelling women attending public events, African-American women were significantly less likely to identify risk factors and treatment options for PFDs when compared to white women.

The patient's lack of knowledge about PFDs has been associated with lack of seeking care for PFDs.[5] Patient knowledge is a barrier to early care, alongside a lack of routine screening by primary physicians. In an email survey of attitudes and knowledge of PFDs among internal medicine and family physicians using a non-validated measure, only half reported screening for UI, and the majority responded that they never screened for POP.[6]

Increasing patient education and physician screening of PFDs may allow for earlier evaluation and treatment of these conditions. In turn, earlier evaluation may allow patients to benefit earlier from conservative options, and lifelong education and behavioral changes that may not be as efficacious at later stages.

Studies have demonstrated that community-dwelling women have a low knowledge proficiency regarding UI and POP. Similar knowledge deficiencies exist in pregnant and postpartum women. The study by Mckay et al highlights that pregnancy may provide a key educational window to help educate women about PFD symptoms, risks, and treatments. As the main providers of prenatal and postnatal care, we are in the unique role of providing women with education and resources regarding PFDs long before they are plagued by their symptoms.

Unsure where to start? Societies such as the American College of Obstetricians and Gynecologists (https://www.acog.org/Patients/Patient-Education-FAQs-List) and the American Urogynecologic Society (https://www.voicesforpfd.org/resources/fact-sheets-and-downloads/) have developed patient information regarding pelvic floor disorders. ■

REFERENCES

1. Mandimika CL, Murk W, Mühlhäuser McPencow A, et al. Knowledge of pelvic floor disorders in a population of community-dwelling women. *Am J Obstet Gynecol* 2014;210:165.e1-9.
2. Shah AD, Massagli MP, Kohli N, et al. A reliable, valid instrument to assess patient knowledge about urinary incontinence and pelvic organ prolapse. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19:1283-1289.
3. Chen CCG, Cox JT, Yuan C, et al. Knowledge of pelvic floor disorders in women seeking primary care: A cross-sectional study. *BMC Fam Pract* 2019;20:doi:10.1186/s12875-019-0958-z.

4. Mandimika CL, Murk W, Mcpencow AM, et al. Racial disparities in knowledge of pelvic floor disorders among community-dwelling women. *Female Pelvic Med Reconstr Surg* 2015;21:287-292.
5. Holst K, Wilson PD. The prevalence of female urinary incontinence and reasons for not seeking treatment. *N Z Med J* 1988;101:756-758.
6. Mazloomdoost D, Westermann LB, Crisp CC, et al. Primary care providers' attitudes, knowledge, and practice patterns regarding pelvic floor disorders. *Int Urogynecol J* 2017;28:447-453.

ABSTRACT & COMMENTARY

Are We Doing Too Many Unnecessary Pelvic Exams and Pap Tests in Young Women?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she receives grant/research support from Bayer, and is a consultant for Bayer, Mylan, and Merck.

SYNOPSIS: In this cross-sectional national survey, the authors estimated that 23% of women aged 15 to 20 years had received a bimanual pelvic exam, of which half (54%) were deemed potentially unnecessary, and 19% of the population received a Pap test, of which 72% were potentially unnecessary.

SOURCE: Qin J, Saraiya M, Martinez G, Sawaya GF. Prevalence of potentially unnecessary bimanual pelvic examinations and Papanicolaou tests among adolescent girls and young women aged 15-20 years in the United States. *JAMA Intern Med* 2020; Jan. 6. [Online ahead of print].

This is a cross-sectional survey using data from the National Survey of Family Growth, a probability-based sample of U.S. men and women aged 15 to 44 years. For this analysis, the population included 3,410 young women aged 15 to 20 years, combining data from 2011 to 2017. The response rate was 70.4%. The following questions were asked, using trained interviewers: 1) "In the past 12 months, have you received a pelvic examination — where a doctor or nurse puts one hand in the vagina and the other on the abdomen?" and 2) "In the past 12 months, have you received a Pap test — where a doctor or nurse put an instrument in the vagina and took a sample to check for abnormal cells that could turn into cervical cancer?" The participants were asked about main reason for the bimanual exam or Pap test and could choose "part of a routine exam"; "because of a medical problem"; or "other reason." The authors classified the bimanual exam as medically indicated if it was associated with pregnancy in the past 12 months, intrauterine device (IUD) use in the past 12 months, receipt of an exam because of a medical problem or other reason, and receipt of treatment for sexually transmitted infections (STIs).

The majority of Pap tests were considered unnecessary because cervical cancer screening is not indicated in women younger than 21 years of age, except for young women who are HIV positive and sexually active. Participants in the survey also were asked if they had been tested for STIs or had been treated or received a medication for STIs in the past 12 months, as well as the type of birth control method used in the past 12 months.

Among U.S. women aged 15 to 20 years, 4.8% were pregnant, 22.3% had undergone STI testing, 4.5% received treatment for an STI, and 2% reported using an IUD during the 2011-2017 study period. The prevalence of ever receiving a bimanual exam was 29%, and the prevalence of receiving a bimanual exam in the past 12 months was 23%. The authors estimated that half of these exams (54%) were potentially unnecessary. One-fifth (19%) of respondents reported receiving a Pap test in the past 12 months. The authors estimated that 72% of these Pap tests were potentially unnecessary. In multivariable analysis, females who used hormonal methods of contraception other than an IUD were 31% more likely to receive a bimanual exam and 75% more likely to receive a Pap test than women not using those methods. Receipt of a Pap test was found to be associated with older age (adjusted prevalence ratio [aPR], 1.54; 95% confidence interval [CI], 1.21-1.96), pregnancy (aPR, 2.31; 95% CI, 1.71-3.11), and IUD use (aPR, 3.77; 95% CI, 2.87-4.95).

■ COMMENTARY

The authors of this study were attempting to estimate how often medical providers were inappropriately performing bimanual exams and Pap tests for women aged 15 to 20 years in the

United States. There are some major limitations in the way the study was performed, which are inherent to national cross-sectional surveys. According to the American College of Obstetricians and Gynecologists, a pelvic examination should be performed when indicated by medical history or symptoms.[1] Otherwise, among asymptomatic women who are not pregnant, the decision to perform a pelvic exam should be a shared decision-making process with the patient and provider. A pelvic examination for screening purposes — for example, to detect ovarian cancer or STIs and pelvic inflammatory disease — among asymptomatic nonpregnant women is controversial.

We lack data on the effectiveness of the pelvic exam for screening. The U.S. Preventive Services Task Force has stated that current evidence is insufficient to assess the balance of risks and benefits of performing a screening pelvic exam in this population.[2] In women younger than 21 years of age, the role of the routine screening pelvic exam is even less relevant. Current recommendations from the Centers for Disease Control and Prevention allow for gonorrhea, chlamydia, and trichomonas screening through self-collected vaginal swabs or urine tests, and a pelvic exam is not required prior to the initiation of contraception other than an IUD.[3,4] In addition, cervical cancer screening does not start until age 21 despite sexual activity in the general population.[5] The concerns regarding unnecessary pelvic exams are the potential harms, which might include anxiety, discomfort, fear, and embarrassment.[1] These harms might be worsened among women with a history of sexual trauma or among adolescents who have never had a pelvic exam before. There is little data on other harms, such as overdiagnosis or overtreatment, due to a bimanual exam, although certainly that can happen with Pap testing.

[Adolescents have been shown to avoid sexually transmitted infection testing and hormonal contraceptive use for fear of having to undergo a pelvic exam.]

In terms of the bimanual exam, the authors estimated about half were potentially unnecessary. It is likely that the participants did understand the question regarding the bimanual exam, since it was very clear, so I would judge their answers as accurate. The limitation comes when the subject may not have realized or remembered that there was a medical indication for the exam according to the medical provider. We have no way of knowing the provider's thought process. In terms of the Pap testing, I see patients all the time who think they have had a Pap test done because a speculum exam was performed. Even though the question is phrased as clearly as possible, many participants may have assumed a Pap test was done when it was not, assuming their doctor should have been checking for cervical cancer. After all, most individuals are not aware that cervical cancer screening does not start until age 21 for the general population.

Furthermore, I do not understand the estimate that only 72% of the Pap tests were potentially unnecessary. That would assume that 28% of the population was HIV positive and sexually active, which is the only indication for Pap testing in women younger than age 21 years. The authors stated that they estimated the prevalence of Pap tests performed as part of a routine examination and considered them potentially unnecessary. I would have assumed the vast majority of the Pap tests would have been unnecessary. Therefore, I think the Pap testing data has some major limitations.

While the numbers in this study may not be entirely accurate, they likely do reflect an overuse of the pelvic exam for adolescents and young women. Adolescents have been shown to avoid STI testing and hormonal contraceptive use for fear of having to undergo a pelvic exam.[6] Therefore, the study reminds us to consider when a bimanual exam and speculum exam are absolutely necessary for patient evaluation. I agree that we need to be judicious in pelvic exam use for adolescents, and certainly follow evidence-based guidelines regarding STI and cervical cancer screening, as well as contraceptive provision. ■

REFERENCES

1. [No authors listed]. ACOG Committee Opinion No. 754: The utility of and indications for routine pelvic examination. *Obstet Gynecol* 2018;132:e174-e180.
2. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. US Preventive Services Task Force. Screening for gynecologic conditions with pelvic examination: US Preventive Services Task Force recommendation statement. *JAMA* 2017;317:947-953.
3. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *MMWR Recomm Rep* 2015;64:1-137.
4. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-66.
5. Committee on Practice Bulletins–Gynecology. ACOG Practice Bulletin No 131: Screening for cervical cancer. *Obstet Gynecol* 2012; 120:1222-1238.
6. Westhoff CL, Jones HE, Guiahi M. Do new guidelines and technology make the routine pelvic examination obsolete? *J Women's Health (Larchmt)* 2011;20:5-10.

ABSTRACT & COMMENTARY

Adverse Perinatal Outcomes Related to Intrahepatic Cholestasis of Pregnancy

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

SYNOPSIS: While a diagnosis of intrahepatic cholestasis of pregnancy is associated with an increased risk for stillbirth, preterm birth, and neonatal respiratory issues, consensus on management within the obstetrics community has not been reached.

SOURCE: Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: Results of aggregate and individual patient data meta-analyses. *Lancet* 2019;393:899-909.

The objective of this systematic review was to clarify the relationship between the range of serum bile acid concentrations and perinatal outcomes (i.e., stillbirth and preterm birth) in pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP). Criteria defining ICP included pruritis and highest recorded total serum bile acid concentration (TBA) in singleton pregnancies. Trials involving at least 30 participants (i.e., no case reports or case series) were included in the analysis along with unpublished data from two United Kingdom hospitals. After criteria were applied, the authors analyzed 23 studies using 5,557 cases of ICP and 165,136 controls.

After review, the authors determined that the overall risk of stillbirth was not increased when compared to controls (odds ratio 1.4; 95% confidence interval, 0.73-2.89). When categorized by highest TBA concentration, stillbirth occurred in 3/2,310 (0.13%) ICP cases with TBAs < 40 µmol/L; 4/1,412 (0.28%) with TBAs 40-99 µmol/L; and 18/524 (3.44%) of cases with TBAs ≥ 100 µmol/L. In comparison, the risk of stillbirth in the control group was 519/163,947 (0.32%). Further assessment of these data indicated that both spontaneous preterm birth and iatrogenic preterm births were increased across all TBA categories from 32-34 weeks gestation and greater, and that preterm births (mostly iatrogenic) occurred in 16.5% of pregnancies with TBAs ≥ 100 µmol/L group and in 8.9% of pregnancies with TBA between 40-99 µmol/L.

The authors concluded that the risk of stillbirth was greatest in pregnant women with ICP whose peak TBAs were 100 µmol/L or greater. This risk began to increase most dramatically around 36 weeks gestation and beyond. Risks of both spontaneous and iatrogenic preterm birth were greater in women with ICP compared to controls, regardless of the TBA concentration.

■ COMMENTARY

Previous studies of ICP have attempted to identify both an ideal gestational age for delivery and a threshold of TBAs that increase the risk of stillbirth.[1] Smaller studies suggest that TBAs > 40 µmol/L are associated with an increased risk of preterm birth[2] and potentially stillbirth,[3] although these studies are limited by small sample sizes and potentially exaggerated risks. Using a large data registry out of California to calculate a composite mortality risk by gestational week in cases of ICP, the ideal time to deliver is 36 weeks. These data do not account for disease severity or TBAs.[2]

[The authors concluded that the risk of stillbirth was greatest in pregnant women with intrahepatic cholestasis of pregnancy whose peak total serum bile acid concentrations were 100 µmol/L or greater.]

This study is meaningful for two reasons. First, the authors painstakingly categorized disease severity and outcomes in more than 5,000 pregnancies affected by ICP. With this detailed stratification, they were able to clarify when adverse pregnancy outcomes were most likely to occur and determined that a TBA of ≥ 100 µmol/L significantly increased the risk of stillbirth. TBAs < 100 µmol/L did not hold this risk. Second, they performed survival analysis (Kaplan-Meir) to determine when the stillbirth (and preterm birth) risks become most significant by week of gestation. TBAs > 100 µmol/L were associated with an increase

in stillbirth risk starting between 35-36 weeks gestation, and this risk continued to increase as gestation progressed. Current recommendations advise for delivery at 36 weeks based on existing, less sophisticated data. It is reasonable that this approach be continued for women with ICP and TBAs ≥ 100 µmol/L. However, for women with TBAs in the 40-99 µmol/L range, stillbirth risks do not appear to increase prior to 38 weeks and, for women with TBAs < 40 µmol/L, stillbirth risks do not appear to increase over the general population. ■

REFERENCES

1. Wikstrom Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: A 12-year population-based cohort study. *BJOG* 2013;120:717-723.
2. Cui D, Zhong Y, Zhang L, Du H. Bile acid levels and risk of adverse perinatal outcomes in intrahepatic cholestasis of pregnancy: A meta-analysis. *J Obstet Gynaecol Res* 2017;43:1411-1420.
3. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology* 2004;40:467-474.

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.

CME/CE QUESTIONS

1. **Analysis of the results of the 2018 Centers for Disease Control and Prevention Breastfeeding Report Card by Bass et al concluded:**
   a. rooming-in immediately after birth increases breastfeeding initiation rates.
   b. the Baby-Friendly Hospital Initiative increases breastfeeding rates at three and six months, but not at 12 months.
   c. sudden, unexpected postnatal collapse is associated with Baby-Friendly accredited programs.
   d. states with high Baby-Friendly designation penetrance did not demonstrate any positive post-discharge breastfeeding association.
2. **Based on the study by McKay et al, pregnant and postpartum subjects:**
   a. are very knowledgeable about urinary incontinence.
   b. are very knowledgeable about prolapse.
   c. lack knowledge about etiology, epidemiology, diagnosis, and treatment of urinary incontinence and prolapse.
   d. did not experience symptoms of incontinence or prolapse.
3. **In the study by Qin et al, what percent of bimanual examinations were considered potentially unnecessary?**
   a. 25%
   b. 54%
   c. 63%
   d. 88%
4. **In the study by Ovadia et al, the risk of stillbirth was significantly increased in which of the following groups with intrahepatic cholestasis of pregnancy?**
   a. Cases with total bile acids (TBAs) < 40 µmol/L
   b. Cases with TBAs 40-99 µmol/L
   c. Cases with TBAs ≥ 100 µmol/L
   d. The control group
5. **Based on data regarding risk of stillbirth and preterm birth in pregnancies affected by intrahepatic cholestasis of pregnancy, which of the following is a reasonable recommendation?**
   a. Any pregnancy with TBAs > 10 µmol/L should be delivered by 36 weeks.
   b. Pregnancies with TBAs ≥ 100 µmol/L should be delivered by 39 weeks.
   c. Pregnancies with TBAs ≥ 100 µmol/L should be delivered by 36 weeks.
   d. Pregnancies with TBAs between 40-99 µmol/L should be delivered by 41 weeks.

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OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

SPECIAL SUPPLEMENT

Long-Lasting, Woman-Controlled Contraception Is Here

By Jeffrey T. Jensen, MD, MPH

Leon Speroff Professor and Vice Chair for Research, Department of OB/GYN, Oregon Health & Science University, Portland

SOURCES: Vieira CS, Fraser IS, Plagianos MG, et al. Bleeding profile associated with 1-year use of the segesterone acetate/ethinyl estradiol contraceptive vaginal system: Pooled analysis from Phase 3 trials. *Contraception* 2019;100:438-444.

Tuazon JP, Sitruk-Ware R, Borlongan CV. Beyond contraception and hormone replacement therapy: Advancing Nestorone to a neuroprotective drug in the clinic. *Brain Res* 2019;1704:161-163.

Gemzell-Danielsson K, Sitruk-Ware R, Creinin MD, et al. Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. *Contraception* 2019;99:323-328.

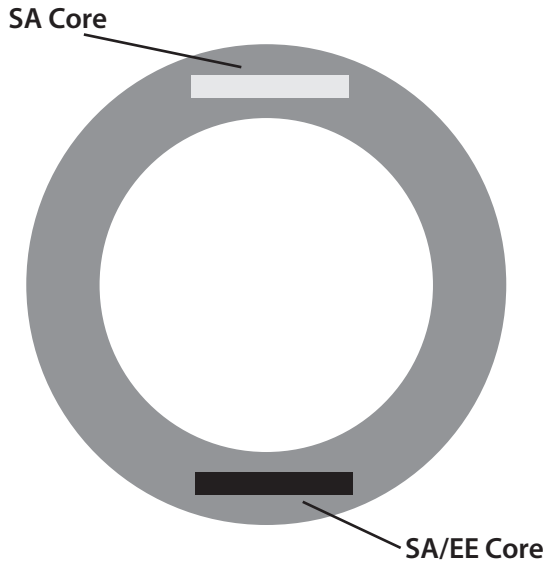
Archer DF, Merkatz RB, Bahamondes L, et al. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: Results of two multicentre, open-label, single-arm, phase 3 trials. *Lancet Glob Health* 2019;7:e1054-e1064.

I decided to introduce the new one-year contraceptive vaginal ring system to you in a special feature to help highlight the most important information about the product in one report. Before I review the data, I want to acknowledge and disclose my relation to this product: I served as a senior advisor to the Population Council on the International Committee for Contraception for much of the ring development program; I served as an investigator in the Eunice Kennedy Shriver National Institute of Child Health and Human Development-funded Contraception Clinical Trial Network (CCTN) that performed the Phase III clinical trial; and most recently, I serve as a consultant for TherapeuticsMD, the small company that will market the ring in the United States. While these opportunities have provided me with a unique inside understanding of this product, they also represent a potential source of influence. Even though these potential conflicts of interest are listed in this publication, I want to be fully transparent about these relationships. My institution, Oregon Health & Science University, also manages potential conflicts of interest for faculty. With that out of the way, let's talk about Annovera.

WHY IS A NEW METHOD NEEDED?

High rates of unintended pregnancy provide evidence that the available contraceptive method mix does not meet the needs of all women. We also know that short-acting methods like oral contraceptives have higher failure rates than long-acting reversible contraceptive (LARC) methods like intrauterine devices (IUDs) or implants. Hubacher and colleagues conducted a partially randomized patient preference trial[1] where they recruited women seeking a short-acting method (pills or injectable) and randomized consenting participants to receive either the short-

Figure 1. Structure of the Annovera Ring



SA: segesterone acetate; EE: ethinyl estradiol

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acting method or a long-acting reversible method of their choice, free of charge. Women who declined randomization were invited to participate in an observational cohort using their preferred method at their own cost. The 12-month method continuation probabilities were similar among the women who received a short-acting method (63% preference short-acting group, 53% randomized short-acting group), but significantly higher (78%) among those randomized to LARC. More impressively, the 12-month cumulative unintended pregnancy probabilities were 6.4% and 7.7% among the preference and randomized short-acting groups, but only 0.7% among those randomized to LARC. This study adds to other convincing population-based research that supports the contraceptive superiority of LARC methods over short-acting methods. LARC uptake has increased substantially over the last two decades,[2] and this correlates with a reduction in unintended pregnancy.[3]

So, it appears we have cracked the nut; increase access to LARC methods, and all women will use them. Only one problem; they won't. Not all women want to use an IUD or implant. Some have had problems with a device, and others balk at the idea of a method that they do not control. In an effort to make use of short-duration methods easier, products like the patch and monthly combination vaginal ring have been introduced. However, these products have not shown greater effectiveness than the Pill.[4] One explanation could be that women have difficulty continuing with a prescription that must be refilled regularly. Pittman and colleagues found that only 30% of participants using short-acting hormonal methods enrolled in the Contraceptive CHOICE Project obtained refills on time, with ring use a predictor of non-adherence.[5] While extended use of the ring may have explained this result, the very low adherence rates support that starting late increases failure rates. So fewer trips to the pharmacy might help. This concept drove the development of the one-year ring.

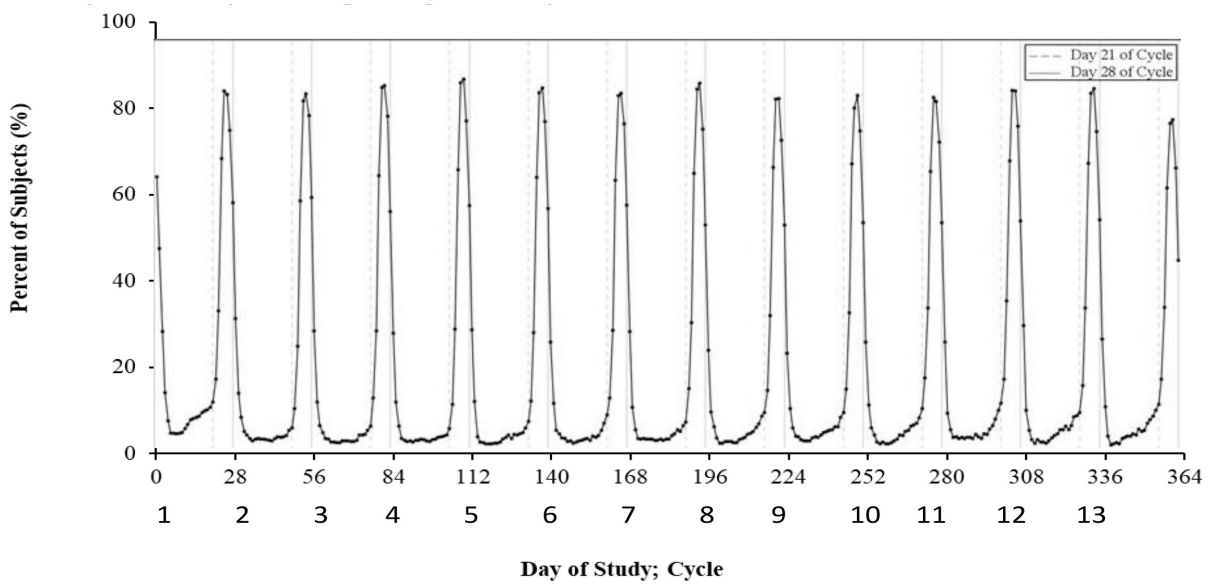
WHAT IS ANNOVERA?

Annovera received U.S. Food and Drug Administration (FDA) approval in August 2018, and a soft market introduction occurred during the fourth quarter of 2019, with full introduction in January 2020. Similar to other combined hormonal methods, the system is designed for 21 days of continuous use, followed by a seven-day ring-free interval, during which the ring is removed, washed, and stored. Unlike other products, the same ring is used for subsequent cycles for an entire year (13 cycles total). Thus, the product represents a new class of "long-lasting" contraceptives. One trip to the pharmacy provides a year of contraception that is woman-controlled.

This system is a soft and flexible silicone elastomer contraceptive vaginal ring (CVR) that is noticeably different from the ethyl vinyl acetate (EVA) monthly ring. Compared to the EVA ring, the silicone material is very soft to the touch and pliable, and not noticed by a woman (or her partner) when correctly placed in the vagina. The CVR has an outer diameter of 56 mm and the cross-sectional diameter is 8.4 mm. The patient places the system in the vagina, directing the ring toward the upper fornix and cervix. Two silicone elastomer cores, 3 mm wide, sealed within hollow channels in the body of the ring, release the contraceptive steroids; one measures 11 mm in length and releases segesterone acetate (SA) and the second core measures 18 mm and releases both ethinyl estradiol (EE) and SA. (*See Figure 1.*) A new CVR contains 103 mg SA and 17.4 mg EE; this provides an average release rate of 150 mcg/day of SA and 13 mcg/day of EE. A major advantage of this CVR over the etonogestrel/EE ring is that it is stable at room temperature and does not require refrigeration. With the 21/7 schedule of use, the same ring is used over 13 consecutive cycles. Release levels of hormones decline gradually over the year of use, but they remain sufficient to provide adequate contraception for several more weeks in the event that a ring is not changed at the correct time.

This product represents the first commercial use of SA, a 19-norprogesterone derivative with reduced binding to the androgen receptor, estrogen receptor,

Figure 2. Percent of Subjects Experiencing Bleeding or Spotting in the Phase III Studies



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and mineralocorticoid receptor compared to 19-nortestosterone derived progestins.[6] SA is not bioavailable following oral administration, so the progestin has been evaluated for delivery as a gel, implant, and ring. SA does not bind sex hormone binding globulin (SHBG) in circulation.[6]

Once released from the ring, SA and EE are absorbed through the vaginal epithelium and enter the circulation through the venous network supplying the upper vagina. Although the vaginal route of delivery avoids first-pass hepatic metabolism, this does not reduce the impact of EE on hepatic globulin production. Therefore, this product carries the same contraindications and thrombosis risk as other combined hormonal contraceptive methods.

HOW EFFECTIVE IS ANNOVERA?

Two identically designed, open-label, single-arm Phase III studies conducted between 2006 and 2009 provide the primary evidence for contraceptive efficacy, bleeding patterns, and safety of the SA/EE CVR. The first study was conducted by the CCTN at 15 U.S. sites, and the Population Council conducted the second international study at 12 sites in the United States, Latin America, Europe, and Australia. The pooled analyses published in *The Lancet* provide the main results for safety and efficacy presented to the FDA,[7] with additional safety data published in *Contraception*.[8]

The primary efficacy endpoint (Pearl Index for women younger than 35 years of age) included 2,265 participants. Forty pregnancies occurred, leading to a calculated Pearl Index of 2.98 (95% confidence interval [CI], 2.13–4.06) per 100 woman-years. Of interest, the Pearl Index was 2.10 among women who did not report any unscheduled ring removals greater than two hours. The Pearl Index was significantly lower among the European participants compared to participants at the other study sites, and also varied by participant age.

WHAT IS THE BLEEDING PATTERN WITH USE OF THIS CVR?

Pooled analysis of bleeding diaries from the Phase III trials included data from 16,408 cycles from 2,070 participants according to World Health Organization (WHO) terminology, with spotting defined as bloody discharge not requiring sanitary protection, normal bleeding defined as flow requiring sanitary protection, and heavy bleeding defined as flow heavier than normal menses.[9] The vast majority of participants reported scheduled bleeding or spotting during CVR use (92-95% per cycle) with a mean of 4.9 ± 1.1 days per cycle and great consistency over the year-long study. (*See Figure 2.*) Only 1.8% of participants discontinued the CVR due to unacceptable bleeding.

WHAT ABOUT SAFETY?

In the Phase III clinical trials, 15 serious adverse events occurred, which were deemed possibly or probably related to the CVR. Four women (0.2%) experienced nonfatal venous thromboembolism (VTE); three had risk factors (two had body mass index [BMI] greater than 29 kg/m^2 and one was found to have Factor V Leiden mutation). Among women with a BMI less than 29 kg/m^2, the VTE rate was

10.8/10,000 woman-years (95% CI, 8.9-13.1). Other serious adverse events included two allergic reactions and 10 spontaneous abortions. Five subjects reported gallbladder disease; one required a cholecystectomy. The general side effect profile appears no different than other combined products.

The occurrence of VTE in obese women during the Phase III trials led to a decision by the Data Safety Monitoring Board to stop enrollment and discontinue participation of obese women. This decision artificially increased the total discontinuation rate for the product during the clinical trial. It also led to the inclusion of special language in the label.

CAN ANNOVERA BE USED IN OBESE WOMEN?

The decision to stop enrollment and discontinue participation of obese women during the Phase III trial resulted in the inclusion of a statement in the package insert in the indications and usage section: Annovera is "not adequately evaluated in females with a body mass index of > 29 kg/m^2." To be fair, most of the combined methods currently on the market have not been adequately evaluated in this high-risk population. The U.S. Medical Eligibility Criteria list use of combined hormonal contraception as category 2 for obese women, and do not distinguish products.[10]

While the available data suggest that the risk of VTE with use of the SA/EE ring will be similar to other combined methods, in our litigious society it makes sense to discuss this controversy with patients considering use of the method. History tells us that new methods attract unhealthy users. I worry that some clinicians may think the vaginal administration of hormones will reduce risks. While this is true for estradiol, vaginal administration of EE still results in an increase in prothrombotic globulins, and the experience with the monthly ring shows a similar risk for VTE. The completion of an FDA-mandated Phase IV post-marketing study for Annovera will provide prospective comparative data similar to studies completed evaluating EE/drospirinone, estradiol valerate/dienogest pills, and the EE/etonogestrel ring. This should clarify this issue, but it is years away.

WHICH WOMEN ARE GOOD CANDIDATES FOR ANNOVERA?

Looking carefully at all of the data, this CVR provides a great option for patients who desire a long-lasting product that is easy to use and woman-controlled. This ring has many advantages similar to LARC methods but does not require clinician placement or removal. One main counseling point requires emphasis: This ring provides highly-effective contraception when it stays in the vagina. In the clinical trials, women who reported any ring removal (except for the seven-day ring-free week) experienced significantly higher failure rates. The explanation is that SA has a very short half-life. While the product label tells women that ring removal for less than two hours does not require back-up contraception, I worry that some women conclude that repeated removal for short intervals is acceptable. The clinical trial results strongly suggest that short-term removal commonly exceeds two hours; it is not hard to imagine how removal for sex could lead to a ring being out overnight. With repeated acts of intercourse, a discontinuous pattern of suppression could lead to follicle growth and ovulation.

No product is good for every woman. In my opinion, women who feel the need to remove the ring for any reason (outside of the scheduled removal week) are not ideal candidates for this method. The ring does not increase the risk of vaginitis and does not require removal for hygiene. Reinforcing this message may encourage perfect use.

The next obvious question would be whether continuous use (no cycle interruption) makes sense. Our experience with other combined methods, including the EE/etonogestrel ring, suggests that continuous use of the SA/EE ring would be acceptable. How this will affect bleeding is not known. I expect that clinical trials will provide better data over the coming years. ■

REFERENCES

1. Hubacher D, Spector H, Monteith C, et al. Long-acting reversible contraceptive acceptability and unintended pregnancy among women presenting for short-acting methods: A randomized patient preference trial. *Am J Obstet Gynecol* 2017;216:101-109.
2. Daniels K, Abma JC. Current contraceptive status among women aged 15-49: United States, 2015–2017. NCHS Data Brief No. 327, Dec. 2018.
3. MacCallum-Bridges CL, Margerison CE. The Affordable Care Act contraception mandate & unintended pregnancy in women of reproductive age: An analysis of the National Survey of Family Growth, 2008-2010 v. 2013-2015. *Contraception* 2020;101:34-39.
4. Sundaram A, Vaughan B, Kost K, et al. Contraceptive failure in the United States: Estimates from the 2006-2010 National Survey of Family Growth. *Perspect Sex Reprod Health* 2017;49:7-16.
5. Pittman ME, Secura GM, Allsworth JE, et al. Understanding prescription adherence: Pharmacy claims data from the Contraceptive CHOICE Project. *Contraception* 2011;83:340-345.
6. Sitruk-Ware R, Nath A. The use of newer progestins for contraception. *Contraception* 2010;82:410-417.
7. Archer DF, Merkatz RB, Bahamondes L, et al. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: Results of two multicentre, open-label, single-arm, phase 3 trials. *Lancet Glob Health* 2019;7:e1054-e1064.
8. Gemzell-Danielsson K, Sitruk-Ware R, Creinin MD, et al. Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. *Contraception* 2019;99:323-328.
9. Vieira CS, Fraser IS, Plagianos MG, et al. Bleeding profile associated with 1-year use of the segesterone acetate/ethinyl estradiol contraceptive vaginal system: Pooled analysis from Phase 3 trials. *Contraception* 2019;100:438-444.
10. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65:1-103.