Beyond Contraception

Liletta examined for extended use, non-contraceptive benefits

Review by Mitchell D. Creinin, MD, and Suji Uhm, MD, MPH

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CHAIRMAN’S LETTER

Reintegrating life

As I write this, some states are figuring out how to reopen their economies and what makes the most sense in the next phase of the COVID-19 pandemic. “New reality” or “new normal” are the phrases being used to capture life as it currently exists and what has been forced upon us. Human beings generally don’t like being told what to do, particularly when it involves restricting their freedom of movement.

But recovery from COVID-19 as a society demands that we all work together for the greater good. In this month’s issue, Editor-in-Chief Catherine Y. Spong, MD, focuses her commentary on what ob/gyns can glean from the “new normal.” As practitioners on the frontlines, how and what are you learning? We want to hear about that. Please email Senior Editor Angie DeRosa at aderosa@mjhlifesciences.com. This issue also marks the return of Resident’s Corner, in which Luke Burns provides a candid view of life on Labor and Delivery during the pandemic.

As is well known among ob/gyns, life will and must go on. Obstetrics never stops. Babies always will be born. As much as COVID-19 is impacting every facet of life, we must continue our coverage on other topics. Our cover story provides an update on the Liletta IUS, which is being studied for 10 years of use in the prospective Phase 3 ACCESS IUS trial. This issue also includes expert insights into how to manage patients who get BRCA results from direct-to-consumer genetic testing. As always, let us know what ob/gyns can glean from the “new normal.” As is well known among ob/gyns, life will and must go on. Obstetrics never stops. Babies always will be born. As much as COVID-19 is impacting every facet of life, we must continue our coverage on other topics. Our cover story provides an update on the Liletta IUS, which is being studied for 10 years of use in the prospective Phase 3 ACCESS IUS trial.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
In “PARP Inhibitors: Choosing what to use in epithelial ovarian cancer,” which appeared in the April issue, several of the reference numbers were coded incorrectly. As a result, the article contained text from some of the research reports that were cited, which should not have appeared. A corrected version of the article is available on our website.
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

DISCOVER A TREATMENT EXPERIENCE WITH SIMPLICITY AT ITS CORE

THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES

PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)

MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED

INDICATION

IMVEXXY (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

• There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens

• Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia

• The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)

• The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Estrogen Plus Progestin Therapy

• Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia

• The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI)

• The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer

• The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

CONTRAINDICATIONS

• IMVEXXY is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

• IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.

• The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

• The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

• Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.

• Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

• Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS

• The most common adverse reaction with IMVEXXY (incidence ≥3 percent) and greater than placebo was headache.

Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following page.


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Estrogen Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.9) in full prescribing information].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]. The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg)-alone, relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information]. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information]. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg) relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.4, 5.15) and Clinical Studies (14.3, 14.4) in full prescribing information]. The WHIMS estrogen plus progestin ancillary study of the WHI reported an overall increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Ovarian Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.83] [see Clinical Studies (14.2) in full prescribing information].

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

Other Warnings and Precautions include:

- Gallbladder disease; severe hypercalcemia; visual abnormalities; elevated blood pressure; hypertensive encephalopathy; hepatic impairment and/or history of cholelithiasis jaundice; hyperthyroidism (women on thyroid replacement therapy may require higher doses of thyroid hormone); fluid retention; hypercalcemia; exacerbation of endometriosis; hereditary angioedema; exacerbation of other conditions (asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas).

ADVERSE REACTIONS

Clinical Trials Experience: In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEXXY (incidence > 3 percent) and greater than placebo was headache.

Post Marketing Experience: The following adverse reactions have been identified during post-approval use of IMVEXXY 4 and 10 mg. Genitourinary System: vaginal discharge.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration.

USE IN SPECIFIC POPULATIONS

IMVEXXY is not indicated for use in pregnancy, in females of reproductive potential, or in children.

Geriatric Use

An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative.
The “new normal” is not normal in any sense of the word. Hearing what our colleagues are going through in areas most affected by COVID-19 is almost beyond comprehension, until we realize that it is actually happening.

We are in a global pandemic, and as ob/gyns in the trenches, our business never stops. Babies will continue to be born, no matter what crisis is ongoing in the world. That said, as many will joke we think it is bad now, imagine what our specialty will be facing in the next 9 to 12 months.

Unlike many physicians in other specialties, ob/gyns are still going to hospitals and offices every day. Our service – at least obstetrics – is business as usual in an otherwise stark hospital, and the complications are compounded rather than diminished. Our pregnant patients are staying home longer to arrive in either the very active stage of labor or with a severe complication that requires immediate attention – adding to the issues to handle as we have no idea of their COVID-19 status and need to use the limited personal protective gear. In an attempt to shield trainees, faculty are thrust into new roles – and then often go home to try to homeschool their children. (On a side note, there is a reason I don’t homeschool my children as I do not have the ability to do this successfully – wish I could – and I will freely admit, this crisis is proving that point).

We all hope that the “new normal” will end soon, but we are faced with an uncertainty of what the next phase of the pandemic may bring. Approaching recovery in phases is key, but we are all coming to the realization that the next phase will not be the “normal” to which we want to return. It will be different. Temperatures will be taken for admittance to facilities at which that would have been unheard of a month ago. Use of personal protective gear may become commonplace; changes to mass transit, entertainment, sporting events, and travel are expected.

During this crisis, my university restricted faculty over age 65 and those with significant medical conditions from having face-to-face encounters with patients. Modeled studies suggest that even in the new normal, it will take years for herd immunity to occur.” That implies that the impact of COVID-19 may reverberate throughout society for at least 2 to 3 years in its impact on this faculty, their families, and our communities. The financial ramifications for practices, especially private practices and those focused on gynecology, may well be significant. The outcome for our specialty is unclear and the tension is constant. Of course, we all have faced variations of “new normal,” such as the changes after 9-11 to travel and airports that were once unfathomable but we now accept as routine. We will work through this together, but to say it is very uncomfortable is an understatement.

As practitioners on the frontlines, we must try to focus on the positive. How and what are we learning? Which of the changes thrust upon us during the pandemic should we keep and which to let go? At my university, we are keeping track of the changes made – as examples: telemedicine visits, longer time between visits, changing indications for sonography and follow-up, indications for admis-
As practitioners on the frontlines, we must try to focus on the positive. How and what are we learning?

The American College of Obstetricians and Gynecologists’ (ACOG) and the Society for Maternal Fetal Medicine (SMFM) clarify CDC’s recommendations on the use of PPE:

ACOG offers COVID-19 FAQs for ob/gyns regarding telehealth:

These companies are offering benefits to ACOG members and residents:

What have you learned so far from managing your patients during this pandemic? How have you used telehealth, for example? What about PPE? Do you have adequate PPE?
Let us know what you think by using the hashtag #covid19 to tweet to @ContempOBGYN.

As practitioners— and identifying metrics to use to determine if they are successful and sustainable. Understanding the impact of these changes on outcomes (stillbirth, maternal and fetal morbidity, gynecologic health, follow-up rates) is critical to determine which to sustain. Some steps we are taking will result in efficiencies and enhance follow-up, while others are merely of necessity. Recognizing that for obstetrics the flow of patients will continue full-fledged (and likely even increase in 9 to 12 months), how to adjust, provide care, and mitigate exposures in the new normal is our next challenge.

Furthermore, rescheduling our gynecology patient visits, cancelled surgeries, and procedures while continuing the current schedule will require collective patience on the part of everyone in the health care system.

As we move to this new normal, we must recognize and empathize with the impact on our patients, colleagues, and their families—especially their mental and physical health. We know from other epidemics that these situations, for those on the frontline and at home, take a major toll. Our patients and patience will be paramount in this new normal we face.

Dr. Spong, editor in chief, is Professor and Vice Chair in the Department of Obstetrics and Gynecology and Chief of the Division of Maternal-Fetal Medicine at UT Southwestern Medical Center in Dallas. She holds the Gillette Professorship of Obstetrics and Gynecology.
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SOURCE
Bacterial Vaginosis & the Risk for Sexually Transmitted Infections

Bacterial vaginosis (BV) affects over 21 million women between the ages of 15 and 44 years in the United States annually, with recurrence rates as high as 58%. Vaginal dysbiosis, which is largely under-studied and misunderstood, is a significant risk factor for acquiring sexually transmitted infections (STIs).

This educational supplement discusses updated treatment guidelines for BV and reviews literature on the association of BV and the risk of STIs that supports the need for proper BV treatment, whether symptomatic or asymptomatic.

Read the supplement contemporaryobgyn.net/vaginosis
HEAVY MENSTRUAL BLEEDING IN ADOLESCENTS
COMMITTEE OPINION #785: Screening and Management of Bleeding Disorders in Adolescents with Heavy Menstrual Bleeding

ABSTRACT
Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss that interferes with a woman’s physical, social, emotional, or material quality of life. If obstetrician–gynecologists suspect that a patient has a bleeding disorder, they should work in coordination with a hematologist for laboratory evaluation and medical management. Evaluation of adolescent girls who present with heavy menstrual bleeding should include assessment for anemia from blood loss, including serum ferritin, the presence of an endocrine disorder leading to anovulation, and evaluation for the presence of a bleeding disorder. Physical examination of the patient who presents with acute heavy menstrual bleeding should include assessment of hemodynamic stability, including orthostatic blood pressure and pulse measurements. The first-line approach to acute bleeding in the adolescent is medical management; surgery should be reserved for those who do not respond to medical therapy. Use of antifibrinolytics such as tranexamic acid or aminocaproic acid in oral and intravenous form may be used to stop bleeding. Nonmedical procedures should be considered when there is a lack of response to medical therapy, if the patient is clinically unstable despite initial measures, or when severe heavy bleeding warrants further investigation, such as an examination under anesthesia. After correction of acute heavy menstrual bleeding, maintenance hormonal therapy can include combined hormonal contraceptives, oral and injectable progestins, and levonorgestrel-releasing intrauterine devices. Obstetrician–gynecologists can provide important guidance to premenarchal and postmenarchal girls and their families about issues related to menses and should counsel all adolescent patients with a bleeding disorder about safe medication use and future surgical considerations.

COMMENTARY
Practical guidance on managing teens with HMB
by PAULA J. ADAMS HILLARD, MD

The American College of Obstetricians and Gynecologists (ACOG) has released a Committee Opinion that addresses a relatively common clinical scenario: that of a teen with excessive menstrual bleeding who may present acutely with syncope or with ongoing prolonged and heavy bleeding.¹ The document highlights the definition of heavy menstrual bleeding (HMB) as excessive menstrual blood loss that interferes with a woman’s physical, social, emotional, or material quality of life. While adolescents in the first few years after menarche (the first gynecologic years) typically have anovulatory cycles that may be somewhat irregular, it is not true that “anything goes” in terms of menstrual bleeding. Adolescent menstrual cycles typically occur in the range of every 21 to 45 days, lasting 7 days or fewer.²

The Committee Opinion provides a screening tool to aid in identifying teens who require further evaluation to determine an underlying cause of HMB, with specific questions about their menstrual history and any other factors that would suggest a bleeding disorder such as von Willebrand disease. Tell-tale signs include soaking the bed sheets and bleeding through a pad or tampon in 2 hours or less. Studies suggest that HMB presenting at menarche is particularly likely to be associated with a bleeding disorder such as von Willebrand disease, most commonly, but also platelet function disorders, thrombocytopenia, and
clotting factor deficiencies.

The adolescent who presents with acute heavy bleeding will require an initial assessment of hemodynamic stability, labs to rule out pregnancy and bleeding disorders, testing for sexually transmitted infections (STI) if a confidential history reveals sexual activity, and consideration of testing for underlying causes of anovulation, as indicated. The next decision in the decision tree is whether inpatient admission is warranted, followed typically by hormonal management, traditionally with a combined oral contraceptive (COC) taper. The authors of the Committee Opinion also note the use of a high-dose progestin taper if there are contraindications to estrogens, although in my own practice, I have switched entirely to use of high-dose progestins followed by a taper, as it is much better tolerated than high-dose COCs.

Typical pitfalls that I see in my referral practice include failure to obtain lab testing for bleeding disorders (prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen, von Willebrand factor activity and antigen, and Factor VIII activity) prior to initiation of hormonal therapy, making interpretation of coagulation studies and von Willebrand testing less accurate if they are tested while the patient is taking hormonal therapy.

The other error that I see frequently is the attempt to stop prolonged, presumably anovulatory, bleeding using a traditional dosing of a one pill/day regimen. This dosing is typically not sufficient to stop the bleeding. The pathophysiology of anovulatory bleeding includes presence of an excessively proliferated or a disordered proliferative endometrium. High-dose hormonal therapy is required to produce cessation of anovulatory bleeding initially, but then a taper and temporary cessation of hormonal treatment is required to shed the thickened endometrium. Following this withdrawal bleeding, which results in shedding of the abnormally proliferated endometrium, maintenance therapy can be initiated with a once-daily pill, given either continuously (recognizing that breakthrough bleeding may still occur) or allowing withdrawal bleeding on a periodic basis. Another management problem that I see in my office is failure to initiate oral iron therapy after an acute bleeding episode, or failure to monitor for problems with adherence to oral iron.

The approach to evaluation of an adult with HMB is modified in adolescents. Per the ACOG Committee Opinion, a speculum examination typically is not required for an adolescent with HMB. Because structural causes of HMB are rare in teens (the PALM causes of HMB in the PALM-COEIN schema’), a pelvic ultrasound is not routinely required, and if deemed necessary because of lack of response to therapy, can typically be performed with a transabdominal approach rather than transvaginal ultrasonography.

Additional pearls that are provided in the ACOG document include the reminder that antifibrinolytics such as tranexamic acid can be used. Although the document cites the prescribing information that lists concurrent use of COCs as a contraindication for these drugs because of a theoretical increased risk of thrombosis, the Committee Opinion notes that data are sparse and these drugs have been used concomitantly when other therapies have been insufficient to control bleeding.

Finally, non-medical options such as use of an intrauterine Foley catheter, suction evacuation of intrauterine clots, or a decidual cast may be appropriate on rare occasions, and when an examination under anesthesia is required, a levonorgestrel intrauterine device may be provided for ongoing therapy of HMB.

Clinicians in practice will undoubtedly see adolescents presenting acutely with HMB. The guidance provided by the ACOG Committee Opinion is well worth noting as a practical reference and guide.

FOR REFERENCES VISIT contemporaryobgyn.net/hmb

What is pediatric and adolescent gynecology? Dr. Hillard shares her expertise in a column online. contemporaryobgyn.net/article/what-pediatric-and-adolescent-gynecology
The last normal place in the hospital

Navigating patient care in L&D during the global COVID-19 pandemic gives one resident cause for pause and reflection. How would it manifest in pregnancy?

by LUKE BURNS

When the first patient suspected of having COVID-19 appeared on L&D, it was like the arrival of a pregnant celebrity. We tiptoed carefully around her room, minimizing our visits as much as possible. We found ourselves constantly hitting the refresh button on her pending SARS-CoV-2 lab result, awaiting confirmation that the coronavirus had finally arrived. Only one physician, the attending, was permitted at the patient’s delivery.

In those early days, the protocols for other COVID-19-positive adults in the hospital were well-established, but the rules for pregnant patients were still being created on the fly. Were new mothers permitted visitors while in labor? Would they be allowed to breastfeed? Would they be permitted to even meet their newborns immediately after birth?

We were not even quite sure how COVID-19 would manifest in pregnancy. Suddenly we were second-guessing all our previous diagnoses. Did the new admit in room 7 really have atypical preeclampsia, or was her isolated thrombocytopenia actually caused by the new coronavirus? That patient with the gastrointestinal bug waiting in triage...should she be tested, too?

Changes to our residency program came swiftly. An emergency meeting was called a few days after the virus hit our state. We were told we would be divided into two teams, with half of the residents scattered into skeleton crews across the hospital and the other half sent home as backup in case anyone was exposed or fell ill.

I already had been working straight through for a couple of weeks when I was told I would be staying for a couple weeks more. Spending so much time in the hospital meant that news about the Coronavirus reached me in bits and pieces. Each morning I would drive to work in the dark and learn on the radio how many people had died during the night. Then each evening as I drove home in the dark, I would learn how many had died during the day.

It turns out that delivering a baby during a global pandemic does not differ much from the days before we had ever heard of COVID-19.

Meanwhile, things on L&D gradually started to change. It seemed like each day brought a new set of rules. In an effort to minimize co-mingling among staff, our anesthesia, midwifery, and family medicine teams stopped attending our normally boisterous morning sign-outs. Suddenly, everyone had to start wearing masks.

LUKE BURNS, MD, is a second-year resident in the Department of Obstetrics and Gynecology at University of Michigan Medicine in Ann Arbor, Mich.
All things considered, however, not much had changed on our floor. It turns out that delivering a baby during a global pandemic does not differ much from the days before we had ever heard of COVID-19. Elective inductions were still going ahead. We did skin-to-skin and delayed cord-clamping. Even the pregnant women who were COVID-19-positive could still have a relatively “normal” birth experience, albeit in a room of people covered head to toe in protective gear.

In fact, it was “on the frontlines” that I felt the most the distant from the pandemic itself. I felt guilty responding to messages from family and old friends, those not in medicine but trapped in their homes by an invisible enemy ravaging their cities and towns. Hey! How is everything going? After getting past the familiarities, So… what’s it like in there?

The truth is, I hardly felt like I was on the frontlines, maybe more front-line-adjacent. If battling COVID-19 is truly the violent conflict our president would have us believe it is, then I felt like I was still a few trenches away from the hand-to-hand combat.

That has not stopped us from adopting the language of soldiers. Residents speak of being deployed to the ICU. Plans are underway for a field hospital. Our daily briefings from administration quote Winston Churchill and urge us to “Stay the course.” The residents outwardly smile at this drama, but each still clings to their N95 mask like it’s a Kevlar vest.

After 3 weeks in the hospital, it was time for me to return home for my pandemic-mandated shore leave. I would be at home for another 2 weeks, enough time for any sign of an infection to manifest itself.

I had been working 14-hour days and overnight weekend call and had only a tangential understanding of how the outside world had changed during that time. It was a shock. When did they close all the restaurants? What over for dinner? What is “Zoom” and how do my parents know how to use it?

The first time someone walking toward me on the sidewalk swerved away to preserve my government-mandated 6 feet of personal space I nearly burst out laughing. Later that day I texted my fiancé from the supermarket, incredulous. Do you know they’ve hired someone whose job is to wipe down all the supermarket carts?

My own sense of hubris started to creep in slowly. At the hospital, passing a sign each day that cheerfully implored me to Thank our healthcare workers!, I had lost touch with the awfulness of this disease. In this otherwise anxious world we now inhabit, it had been wonderful to do something as joyful as deliver babies every day.

All the while, three floors above me, patients were dying on ventilators. It was only after I left the wards that I really began to be afraid of COVID-19.

IT WAS ONLY AFTER I LEFT THE WARDS THAT I REALLY BEGAN TO BE AFRAID OF COVID-19.

AFTER I WAS ABLE TO STEP BACK AND SEE THE BAS-RELIEF IMPRESSION IT HAD LEFT IN THE WORLD OUTSIDE OF THE HOSPITAL.
A package of nine individual bills has just been introduced that aim to improve health for black mothers in the United States. “Black Maternal Health Momnibus Act of 2020” is led by Senator Kamala D. Harris (D-CA) and Representatives Lauren Underwood (IL-14) and Alma Adams (NC-12). All three are members of the Black Maternal Health Caucus, founded in 2019 to improve black maternal health outcomes.

Statistics show that black women are nearly four times more likely than white women and more than twice as likely as women of other races to die from preventable, pregnancy-related complications. They also experience higher rates of maternal complications and infant mortality.

The Act is designed to fill gaps in existing legislation to comprehensively address every dimension of the black maternal health crisis in the nation. If passed, the bills included in it will result in the following:

- Critical investments in social determinants of health that influence maternal health outcomes, such as housing, transportation, and nutrition;
- Funding for community organizations working to improve maternal health outcomes for black women;
- Comprehensive study of the unique maternal health risks facing women veterans and investment in Veterans Administration maternity care coordination;
- Growth and diversification of the perinatal workforce to ensure that every mother in America receives maternity care and support from people she can trust;
- Improved data collection processes and quality measures to better understand the causes of the maternal health crisis in the United States and inform solutions to address it;
- Investment in treatments for maternal health care and substance use disorders;
- Improved maternal health care and support for women who are incarcerated;
- Investment in digital tools like telehealth to improve maternal health outcomes in underserved areas; and
- Promotion of innovative payment models to incentivize high-quality maternal care and continuity of health insurance coverage from pregnancy through labor and delivery and up to 1 year postpartum.

Among the over 100 organizations endorsing the Act are the American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, American College of Nurse-Midwives, and Planned Parenthood.

Said Senator Harris in a press release about the legislative package, “Black women across the country are dying from pregnancy and childbirth complications at astounding rates and the disparity transcends income and education levels. It is critical that the federal government work with states, local health providers, and mothers and their families to address the crisis and save lives.”

Judith M. Orvos, ELS is an editorial consultant for Contemporary OB/GYN.

SOURCE
Inflammatory bowel disease and pregnancy outcomes

by JUDITH M. ORVOS, ELS

A new systematic review and meta-analysis suggests that women with inflammatory bowel disease (IBD) may be at increased risk of adverse pregnancy outcomes such as gestational diabetes mellitus (GDM) and preterm premature rupture of membranes (PPROM). The authors caution, however, their results need to be confirmed in larger, prospective studies.

Published in *Alimentary Pharmacology & Therapeutics*, the findings are by Canadian researchers who searched Medline, Embase, and the Cochrane library through May 2019 for studies reporting adverse maternal, placental and obstetric outcomes in patients with IBD. Nearly 8000 pregnancies complicated by IBD and more than 3,200 control pregnancies were represented in the 53 studies selected for analysis.

The authors hypothesized that women who took medication for IBD during pregnancy might have an increased risk of adverse outcomes such as cesarean delivery, GDM, preeclampsia, chorioamnionitis, placental abruption, PPROM, early pregnancy loss, elective termination of pregnancy, termination of pregnancy, and ectopic pregnancy. The medications considered were 5-aminosalicylates (5-ASA), corticosteroids, thiopurines, anti-tumor necrosis factor (TNF) therapy, vedolizumab, ustekinumab, and tofacitinib.

Analysis of the data from the studies showed that cesarean delivery was more common in patients with IBD compared to healthy controls (OR 1.79, 95% CI 1.16 to 2.77). This remained significant for ulcerative colitis but not Crohn’s disease (OR 1.48, 95% CI 0.94 to 2.34). GDM also was more common in women with IBD (OR 2.95, 95% CI 1.47 to 5.98).

Incidences of placental disease were 2.0% (95% CI 0.9% to 3.1%) for pre-eclampsia, 3.3% (95% CI 0% to 7.2%) for placental abruption, 0.5% (95% CI 0.2% to 0.9%) for placenta previa and 0.3% (95% CI 0% to 0.5%) for chorioamnionitis. Women with IBD were more likely to experience PPROM (OR 12.10, 95% CI 2.15 to 67.98) but not early pregnancy loss (OR 1.63, 95% CI 0.49 to 5.43).

Anti-TNF therapy was not associated with chorioamnionitis (OR 1.12, 95% CI 0.16 to 7.67), early pregnancy loss (OR 1.49, 95% CI 0.83 to 2.64) or placenta previa (OR 1.58, 95% CI 0.30 to 8.47). The authors noted, however, that the study sample sizes were small and control group comparisons were lacking so definitive conclusions about the drugs cannot be made. They are, however, in line with recent guidelines from the American Gastroenterological Association to continue anti-TNF therapy in pregnant women to maintain IBD remission.

**SOURCE**

How are miscarriages discussed on social media?

by BEN SCHWARTZ

Miscarriages and preterm birth (PTB) can be a difficult experience for expectant mothers, and many seek out positive support systems to help cope. As the world has become more digital, social media has become a support system for women who have experienced these events, according to new research published in *Paediatric and Perinatal Epidemiology*. The study aimed to better understand how Twitter users discuss the topics of miscarriage and PTB, analyze the trends and drivers, and describe the perceived emotional state of women who have

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experienced a miscarriage. The authors obtained 291,443 Twitter posting on miscarriages and preterm births from January 2017 through December 2018. They applied Latent Dirichlet Allocation (LDA) to identify major topics in the data. LDA models are used for uncovering latent topics within a large set of text. Words are assigned weights within particular topics given assumed probability distributions. The authors also used time series decomposition methods to assess temporal trends and identify major conversation drivers. In order to determine the emotional content of 7282 personal miscarriage disclosure tweets, the authors classified the tweets into six non-mutually exclusive categories: grief/sadness/depression, anger, relief, isolation, annoyance, and neutral. Based on their findings, the authors discovered that the topics in their data fell into eight groups: celebrity disclosures, Michelle Obama’s disclosure, politics, healthcare, preterm births, loss and anxiety, flu vaccine and ectopic pregnancies. However, they noted that the political discussions around miscarriages were largely a result of a misunderstanding between abortions and miscarriages. Within miscarriage disclosures, grief and annoyance were the emotions most commonly expressed by users 50.6% (95% CI 49.1 – 52.2) and 16.2% (95% CI 15.2 to 17.3), respectively. The authors also noted that postings increased with celebrity disclosures; celebrities were considered strong and brave for publicly discussing the topic and Michelle Obama’s disclosure generated substantial response. These celebrity disclosures also led to increased disclosures by women who had similar experiences. For example, Obama’s disclosure resulted in a response approximately 3.6 times higher than the weekly average of postings in 2018. Postings also increased with pharmacists’ refusal of prescribed medications and with outrage over the high rate of preterm births in the United States. Based on the results of their study, the authors believe that celebrity disclosures lead to the biggest increase in discussions of miscarriage on social media. They also believe that the results provide an insight of current public perceptions of miscarriage and illustrate how individuals use Twitter to share information and/or seek support. A better understanding of how individuals who have experienced miscarriage use social media may be informative for clinicians who provide miscarriage care and treatment.

Ben Schwartz is the former associate editor for Contemporary OB/GYN.

SOURCE

Even as she herself was recovering from what she qualified as a “mild” case of COVID-19, Dr. Riley shared her expert perspective with Senior Editor Angie DeRosa on the impact the coronavirus is having in pregnant patients and steps to be taken. Dr. Riley is chair of the department of Obstetrics and Gynecology at Weill Cornell Medicine and Obstetrician and Gynecologist-in-chief at New York Presbyterian/Weill Cornell Medical Center.

FOR INSIGHT INTO MANAGING COVID-19 AMONG PATIENTS WHO ARE PREGNANT, CHECK OUT THE INTERVIEW WITH DR. LAURA RILEY ONLINE AT www.contemporaryobgyn.net.

Dr. Riley is a renowned obstetrician who specializes in obstetric infectious diseases.
While cervical ripening — used to facilitate the softening and thinning of the cervix — was primarily initially confined to the inpatient setting, outpatient cervical ripening has now become the standard of care in many countries. It has, however, been more slowly adopted in the United States.

In this *Contemporary OB/GYN* supplement, four ob/gyn experts discuss the reasons for the divergent perspective and offer insight into why outpatient cervical ripening may or may not be appropriate for today’s pregnant women.

**Go to:**
contemporaryobgyn.net/across-borders
Liletta IUS: not just for long-term contraception

by MITCHELL D. CREININ, MD, AND SUJI UHM, MD, MPH

Introduction

Of women using reversible contraception in the United States, 16% use an intrauterine device (IUD) equaling 4.4 million women in 2014.1,2 Today, five IUDs are available: Paragard®, a non-hormonal copper IUD, and four hormonal intrauterine system (IUS) products containing levonorgestrel – Liletta®, Mirena®, Kyleena® and Skyla®. These systems are categorized by the amount of levonorgestrel that they contain —52, 19.5 or 13.5 mg. The amount of hormone drives the efficacy, bleeding profile, and recommendations for length of use. The 52-mg IUS has gained popularity as a highly effective, reversible contraceptive because of several advantages, including the ability to significantly decrease menstrual blood loss and improve dysmenorrhea. The US Food and Drug Administration’s first approval of a 52-mg IUS was for Mirena for a 5-year duration. In 2009, an indication for treatment of heavy menstrual bleeding was added.3 The second levonorgestrel 52-mg IUS, Liletta, was initially approved for 3 years for contraceptive use in 2015 and, as of October 2019, is approved for up to 6 years.4 The drive to bring Liletta to market as a second levonorgestrel 52-mg IUS was based on cost barriers. Unintended pregnancies, unintended births, and abortions are disproportionately high in women of low socioeconomic status (SES).5 While reasons for these findings are multifactorial, there is an established relationship between low SES and less effective use of contraception.5 When cost is removed as a barrier, use of long-acting reversible contraception (LARC) increases dramatically.1,6,7 Under the Health Resources & Services Administration (HRSA), manufacturers participating in Medicaid can provide drugs at significantly reduced prices to eligible organizations/entities under the 340B Drug Pricing Program.8 Medicines360, the non-profit women’s health pharmaceutical company that brought Liletta to the US market, participates in the 340B Program and offers a price approximately three times lower than for Mirena.9,10 This significantly lower cost puts less burden on clinics and providers to stock the device and allows immediate access, which can help eliminate the need for multiple visits for IUD insertion.11 Immediate access improves IUD utilization, especially in women with public insurance, who will only receive an IUD about half the time when two visits are required.11 A real-life assessment of this lower-cost levonorgestrel 52-mg Liletta is under study in a prospective phase 3 clinical trial aimed at extending the approved duration of this levonorgestrel 52-mg IUS.
IUS option at several Title X clinics in Utah resulted in an immediate increase in uptake. The low cost is financially supported through private sector sales, a model like the Toms Shoes and Bombas socks, wherein private sector sales support the ability for low or no cost in the public sector. As a medical community, this opportunity allows all providers to participate in efforts to provide equitable care and expand access. Liletta has a T-shaped polyethylene frame with the same dimensions as Mirena. The inserters differ slightly; the reloadable Liletta inserter is 2 cm longer than the non-reloadable Mirena one, and the Mirena inserter is slightly narrower than the Liletta inserter (4.3 mm vs. 4.8 mm). Despite these differences, reported successful insertion rates from phase 3 trials are 98% to 99% for both products. Liletta produces an initial release rate of 19.5 µg/day, which decreases slowly over time to 9.8 µg/day at the end of 5 years, mirroring the release rate of Mirena. For comparison, the levonorgestrel 13.5-mg IUS release rate at the end of its 3-year duration is 5 µg/day. The calculated estimated release rates based on this information support using Liletta for contraception beyond 5 years. Liletta is under study in a prospective phase 3 clinical trial aimed at extending the approved duration of the levonorgestrel 52-mg IUS and evaluating the potential non-contraceptive benefits or side effects of the device among a diverse US population. This review provides key findings of the ongoing clinical trial and important discussion points that can be referenced during patient counseling to augment the shared decision-making process in contraceptive method selection.

ACCESS IUS: A Comprehensive Contraceptive Efficacy and Safety Study of an IUS

ACCESS IUS was designed to assess the efficacy and safety of Liletta among a diverse population of women in the United States. It is a multicenter, phase 3, open-label clinical trial conducted at 29 sites in the United States including public, private, and university institutions. Of 1751 women, 1600 participants were aged 16 to 35 years and included in efficacy assessments and 151 participants aged 36 to 45 years were included for overall safety evaluation. The primary outcome was on-treatment pregnancy, defined as any pregnancy with a date of conception beginning with the day of Liletta placement and through 7 days after IUS discontinuation.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of pregnancies</th>
<th>Pearl Index individual year (pregnancies/100 women-years [95% CI])</th>
<th>Life-table pregnancy rate [% (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.15 (0.02-0.55)</td>
<td>0.14 (0.04-0.57)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.37 (0.10-0.94)</td>
<td>0.49 (0.22-1.09)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.11 (0.00-0.62)</td>
<td>0.59 (0.28-1.25)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.13 (0.00-0.73)</td>
<td>0.72 (0.36-1.45)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.16 (0.00-0.87)</td>
<td>0.87 (0.44-1.70)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.00 (0.00-0.94)</td>
<td>0.87 (0.44-1.70)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval
Adapted with permission from Westhoff C, et al. Contraception. 2020;101(3):159-161.
Contraceptive efficacy through 6 years

Of the 1751 women enrolled, successful placement among women who had attempted IUS placement was 98.7%.

Reasons for unsuccessful placement included inability to sound the uterus (n=15, 0.9%) and uterine measurement by sounding less than 5.5 cm (n=2, 0.1%). There were two pregnancies in the first year – one intrauterine pregnancy after Liletta IUS expulsion and one ectopic pregnancy associated with a uterine perforation. The Pearl Index (number of pregnancies per 100 woman-years) is 0.15 (95% CI 0.02 – 0.55) through year 1. By the end of the fifth year, there were nine total pregnancies in over 1500 women, representing over 6300 28-day cycles. Of the nine pregnancies, six were ectopic, resulting in an ectopic pregnancy rate through 5 years of 0.13 per 100 woman-years. There were no pregnancies reported year 6. Pregnancy rates are presented in Table 1. Based on these data, the FDA approved Liletta to be utilized for pregnancy prevention for 6 years in October 2019, and the study is ongoing through 10 years of IUS use.

Bleeding and amenorrhea rates using Liletta

In addition to its high efficacy in pregnancy prevention, Liletta has also been extensively studied to evaluate its bleeding profile during use. Amenorrhea secondary to hormonal contraception is often a desirable characteristic, as evidenced in the ACCESS IUS trial in which only one participant discontinued Liletta (in year 2 of use) due to amenorrhea.

Mirena is reported to have a 20% amenorrhea rate in the first year of use but generalizability is limited due to the skewed population of normal-weight, multiparous, white women who had used an intrauterine method previously. So, investigators used the ACCESS IUS data to evaluate amenorrhea and bleeding patterns in detail over the first year of use. In the first year, 28 women (1.8%) discontinued levonorgestrel IUS use for bleeding complaints. Among women who had not previously used a levonorgestrel IUS, amenorrhea rates were 17%, which was the same rate at 9 and 12 months. Among women using a levonorgestrel IUS prior to enrollment, the amenorrhea rates are 35% at 9 and 12 months. Amenorrhea rates in levonorgestrel 52-mg IUS users continue to rise over 6 years. At the end of 2 and 3 years, 27% and 36% of users reported amenorrhea the previous 90 days of years 2 and 3, respectively. The rate remains about 40% in years 4, 5, and 6.

Levonorgestrel 52-mg IUS use is also notable for other decreased uterine bleeding patterns. Because these bleeding patterns can be more subjective, the Besley definitions provide an objective guide for measurements of change over time (Table 2). Prevalence of amenorrhea and infrequent, frequent, irregular, and prolonged bleeding are described in Table 3. It is common for users to experience frequent, irregular, and/or prolonged bleeding during the first 3 months, which transitions to less frequent, less

| Table 3 | Bleeding patterns with levonorgestrel 52-mg IUS over time for the first 2 years of use |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics | 3 months | 6 months | 1 year | 2 years |
| Amenorrhea | < 1% | 11% | 19% | 27% |
| Infrequent bleeding | 14% | 25% | 31% | 30% |
| Frequent bleeding | 26% | 9% | 5% | 4% |
| Irregular bleeding | 38% | 14% | 6% | 4% |
| Prolonged bleeding | 51% | 10% | 5% | 2% |

prolonged bleeding by 6 months and beyond (Table 3). While direct comparisons between IUS products with different levonorgestrel amounts are difficult due to varied study designs and populations, both levonorgestrel 13.5-mg and 19.5-mg IUS devices are noted to have lower rates of amenorrhea and infrequent bleeding compared to the 52-mg IUS. This bleeding pattern information is essential for providing accurate information for patients considering levonorgestrel 52-mg IUS use.

Mirena is currently indicated for treatment of heavy menstrual bleeding (HMB) in the United States and Liletta carries the same indication in all countries other than the United States. Lilletta use increases hemoglobin and serum ferritin levels, and in a randomized trial comparing Mirena and Lilletta over 12 months in women with HMB, there were no differences in mean blood loss, ferritin, or hemoglobin values between the two products. HMB is quantitatively defined as ≥ 80 mL per cycle, but subjective perception of it is commonly used for diagnosis in clinical practice. Bleeding changes in women who subjectively report HMB have been evaluated in Lilletta users. Among women using Lilletta for contraception who self-report HMB at baseline, 75% reported absence of it by the end of the first cycle (28 days). By 6 months, 92% reported absence of HMB, which rose to 97% at the end of 2 years. By 1 and 2 years, 51% and 64%, respectively, reported their bleeding as amenorrhea or spotting.

Because women can experience many events over years of use, discontinuation is a more tangible outcome to evaluate. Overall, in subjects followed for up to 8 years of use, 329 (19.2%) discontinued the study due to an AE. Because women can experience many events over years of use, discontinuation is a more tangible outcome to evaluate. Overall, in subjects followed for up to 8 years of use, 329 (19.2%) discontinued the study due to an AE. The most common AEs leading to discontinuation and their frequencies are listed in Table 4. Partial or complete expulsion was the most common reason, occurring in 4% of Lilletta users, 73% of which occurred during the first year of IUS use. Expulsion rates were similar to previously reported values and three times more common in multiparous compared to nulliparous individuals. Overall, only 8.4% of women in the Lilletta trial discontinued for a non-expulsion AE. The most common events (≥ 1%) were bleeding complaints, acne, dysmenorrhea, and weight increase. Of note, ovarian cysts had been commonly reported in Mirena trials, primarily because those studies included enlarged asymptomatic cysts which were identified during required study ultrasound evaluations. The Lilletta trial only evaluated symptomatic women, reporting an ovarian cyst in 78 participants (4.5%), of whom only six (0.3%) requested IUS removal. One (0.06%) of the ovarian cysts identified required surgical intervention.

Another important observation from this trial is the very low risk of infection with contemporary IUS insertion practice. In this prospective trial, participants could have same-day Lilletta placement and did not have to defer for sexually transmitted infection (STI) testing results. Investigators treated IUS users found to have positive testing after IUS insertion. Pelvic infection was diagnosed in 14 participants (0.8%) during up to 8 years of follow-up, including two diagnosed after year 4. These results further support same-day IUS insertion and outpatient antibiotic treatment for positive test results without concurrent removal of IUS and overall very low risk of infection with extended use.

**Conclusions**

ACCESS IUS is a robust, ongoing phase 3 clinical trial that continues to update clinicians about Lilletta. Trial investigators have reported efficacy rates up to 6 years, which is the current FDA-approved duration, with plans to continue the study to provide data through 10 years. Prospective data improve the understanding of bleeding patterns, including amenorrhea rates,
Results from a longitudinal study suggest that bacteria in the cervicovaginal microbiome (CVM) may play a role in risk of progression of high-risk human papillomavirus (HR-HPV) to cervical precancer. If the connection is validated in future studies, it could hold promise for development of microbial biomarkers for progression risks of HR-HPV to cervical intraepithelial neoplasia 2 (CIN2).

Published in *PLoS Pathogens*, the findings are from a nested study within the placebo arm of the Costa Rica HPV Vaccine Trial, which included women aged 18 to 25. The authors looked at the prospective role of the CVM on the natural history of HR-HPV by assessing cervical samples from 273 women with HR-HPV taken during two visits. Their focus was on infection clearance, persistence, and progression to CIN2 and CIN3.

Analysis of the samples from Visit 1 showed that an abundance of *Lactobacillus iners* was associated with clearance of incident HR-HPV infections (Linear Discriminant Analysis [LDA] > 4.0) whereas *Gardnerella* was the dominant biomarker for HR-HPV progression (LDA > 4.0). At Visit 2, increased microbial Shannon diversity was significantly associated with progression to CIN2 ($P = 0.027$).

Multivariate analysis showed that the positive association between *Gardnerella* and CIN2 progression was a result of the increased cervicovaginal diversity seen in the swabs from Visit 2. A full multivariate model of key components of the CVM showed significant protective effects via Visit 1 genus *Lactobacillus* (OR = 0.41 [0.22 to 0.79]), fungal diversity (OR = 0.90 [0.82 to 1.00]) and functional cell motility pathway (OR = 0.75 [0.62 to 0.92]) whereas Visit 2 bacterial diversity (OR = 1.19 [1.03 to 1.38]) was shown to be predictive of progression to CIN2.

The authors said of their data on *Gardnerella* that "rather than directly causing the CIN2+ lesions, [it] appears to induce a higher diversity CVM over time as measured at V2 which in turn mediates the observed effect of *Gardnerella* in HR-HPV disease progression." Further, “the association may be tied to the ability of *Gardnerella* to be immunosuppressive in the cervicovaginal region. Whereas, it seems that the presence of commensal bacteria (e.g. *Lactobacillus*) with the ability to stimulate a local immune response may be contributing factors to the clearance of incident HR-HPV infections.”

Additional prospective studies are needed, the researchers concluded, to establish a causal link between the CVM, the immune system, and the natural history of HPV.

*Judith M. Orvos, ELS,* is an editorial consultant for Contemporary OB/GYN.

**SOURCE**


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**How prevalent is HPV in vaccinated adolescents?**

[contemporaryobgyn.net/hpv/how-prevalent-hpv-vaccinated-adolescents](contemporaryobgyn.net/hpv/how-prevalent-hpv-vaccinated-adolescents)

**HPV home testing: First US Trial**

[contemporaryobgyn.net/cervical-cancer/hpv-home-testing-first-us-trial](contemporaryobgyn.net/cervical-cancer/hpv-home-testing-first-us-trial)

**Examining the impact of HPV vaccination**

[contemporaryobgyn.net/hpv/examining-impact-hpv-vaccination](contemporaryobgyn.net/hpv/examining-impact-hpv-vaccination)
New research published in *Obstetrics & Gynecology* indicates that risk of high-grade cervical neoplasms is lower with copper (Cu) intrauterine devices (IUDs) than with the levonorgestrel-releasing intrauterine system (LNG-IUS). More than 100 million women worldwide use IUDs as contraception so these findings could have global implications.

The current study was a retrospective cohort analysis of 10,674 patients who received IUDs at Columbia University Medical Center. The authors restricted their cohorts to women age 45 years or younger at time of IUD insertion. Patients with a history of endometrial or cervical neoplasms or who had a prior IUD placement were excluded.

By default, women were in the Cu IUD cohort unless documentation of LNG-IUS appeared in the database. The outcome of the study was high-grade malignant cervical neoplasm or cervical neoplasm with a high association with malignancy, such as cervical intraepithelial neoplasia (CIN) grade II or III. Cervical polyps, CIN grade I, and metastatic spread of neoplasm to the cervix were excluded. Patients in the cohort and their outcomes were identified by a combination of procedure codes, condition codes, and medication exposures in billing and claim data. The authors adjusted for confounding with propensity score stratification and 1:1 matching.

A total of 10,674 patients were studied. Of them, 8,274 patients were in the Cu IUD cohort and 2,400 were in the LNG-IUS cohort. Ninety-seven percent (2,332) of the LNG-IUS users received a 52-mg device. Median age was 29 years (range 24-35) years in the Cu IUD cohort and 28 years (23-34) in the LNG-IUS cohort. During follow-up, 1,820 (22.0%) Cu IUD users and 797 (33.2%) of LNG-IUS users had a documented IUD removal procedure.

Before propensity score adjustment, the authors identified 114 cases of cervical neoplasm: 77 (0.9%) in the Cu IUD cohort and 28 (3.5%) in the LNG-IUS cohort. During follow-up, 1,820 (22.0%) Cu IUD users and 797 (33.2%) of LNG-IUS users had a documented IUD removal procedure.

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The authors noted that the association between IUD usage and high-grade cervical neoplasm incidence has implications for public health on a global scale because more than 100 million women worldwide use the devices for contraception. The approximate 1% difference in high-grade cervical neoplasm incidence between Cu IUD and LNG-IUS user could have a large effect, especially in areas with the highest incidence of cervical cancer.

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**Does IUD type impact cervical cancer risk?**

*by Ben Schwartz*

**WE WANT TO HEAR FROM YOU**

Want to let *Contemporary OB/GYN* know what you thought of this month’s cover story? Feel like telling Dr. Spong what you thought of her editorial or how your practice is responding to COVID-19?

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A diagnosis of vulvovaginal atrophy (VVA) in breast cancer survivors is associated with a significant increase in the burden of illness and social costs, according to an Italian Delphi Panel in the journal Supportive Care in Cancer. These findings are primarily due to a rise in comorbidities and resource utilization, but adequate treatment might reduce the impact of the condition.

Affecting roughly 50% of all postmenopausal women, VVA is magnified by longer life expectancy, with many women spending more than one-third of their life in the postmenopausal state. However, despite the substantial negative impact it has on quality of life, there is a disparity between VVA’s high prevalence and infrequent clinical diagnosis, which has been documented in medical practice and in surveys.

In large part, this discrepancy is believed to be the result of patients unwilling and/or reluctant to report symptoms in the clinical setting and the difficulty healthcare professionals have in approaching this sensitive topic during routine consultations. “The result of this underdiagnosis is a chronic condition that may not be addressed for a long time and, therefore, is more likely to undergo progression when left untreated,” the Italian authors wrote.

The Delphi Panel, which was conducted in response to the lack of published evidence on VVA in Italy, evaluated the epidemiology of VVA; the risk factors/comorbidities; the current standard of care and unmet medical needs; the comparison between recent US epidemiological data and the Italian patient population; and the health resources used for VVA and breast cancer.

The panel estimated that the prevalence of VVA is 115,000 cases out of 380,000 breast cancer survivors.

The Panel also collected information on the experience of participants with new treatments for VVA, such as ospemifene, and how these treatments are perceived in their capability to reduce symptoms associated with VVA. A questionnaire was sent via email to all participants in Italy in November 2016, followed by a 1-day panel convened in Milan on November 24, 2016. Two additional rounds of follow-up interviews took place in January and July 2017, with final analyses completed in December 2018.

The panel estimated that the prevalence of VVA is 115,000 cases out of 380,000 breast cancer survivors. They also confirmed that the epidemiological findings of a 2014 pharmacoeconomic analysis of a US claims database are applicable to the Italian patient population.

Furthermore, the panel verified an estimated 4.25 additional cases/100/year of urinary tract infection (UTI), 3.68 additional cases of vulvovaginitis, 6.97 additional cases of climacteric symptoms and 3.64 additional cases of bone and joint disorders in breast cancer patients with VVA compared to a non-VVA-matched population.

The panel was also unanimous in stating that depression and the need for psychological counseling are more frequent in VVA patients, and more severe in those who have a history of breast cancer.

To meet the medical needs of the VVA breast cancer population, 33.4 additional gynecological visits/100/year can be anticipated, along with 22.8 additional cancer screenings, 7.07 additional outpatient visits and 5.04 screenings for human papillomavirus.

“In particular, vaginal laser have shown a beneficial effect in treating VVA in breast cancer survivors in the short term, but there is no sufficient data on the long-term treatment,” the authors wrote, whereas ospemifene has demonstrated clinical safety on the breast tissue and thus may be appropriate in women with a previous history of breast cancer.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

FOR REFERENCES VISIT contemporaryobgyn.net/vvatrophy
Impact of vulvovaginal atrophy on sexual function in postmenopausal women

by BOB KRONEMYER

For postmenopausal women with at least one vulvovaginal atrophy (VVA) symptom, the presence of physician-confirmed VVA is linked to significant impaired sexual function, according to a study from the European Vulvovaginal Epidemiological Survey (EVES). Published in Menopause, it showed that the two most common symptoms of impaired sexual function with VVA are dryness (87.6%) and pain during intercourse (66.8%).

“VVA is chronic, progressive with age and with hormonal deprivation, which is associated mainly with low estrogens with menopause, but also a slight decline of androgen with age,” said principal investigator Rossella Nappi, MD, PhD, a professor of ob/gyn at the University of Pavia in Italy. “VVA affects around 50% of postmenopausal women and has a dramatic impact on sex and quality of life. However, it is largely undiagnosed and undertreated, due to lack of communication and poor recognition of the burden in daily practice.”

Dr. Nappi has attempted to understand how to fill this gap, but most importantly how to help women recognize the symptoms of VVA and assist healthcare providers in detecting the signs, in order to tailor the right treatment. The survey queried 2,403 evaluable women, ranging in age from 45 to 75 (mean 59.0 years and being menopausal for 9.9 years), between May 2015 and March 2016, of whom 2,160 had at least one symptom related to VVA. All participants attended one of 46 menopausal/gynecological centers in Italy and Spain and had their last menstruation more than 12 months prior. The women completed the following three questionnaires: Day-to-Day Impact of Vaginal Aging (DIVA), Female Sexual Function Index (FSFI), and Female Sexual Distress Scale revised (FSDS-R).

The negative impact on sexual function was significantly higher in women with confirmed VVA than in women without confirmed VVA, as evaluated with the sexual function component (DIVA-C) of the DIVA questionnaire ($P = 0.013$).

Statistically significant differences ($P < 0.0005$) were also detected in the scores for overall FSDS-R, overall FSFI and for all six FSFI subdomains: desire, arousal, lubrication, orgasm, satisfaction, and pain.

In addition, 65.9% of the overall cohort was currently sexually active. “But there was a nonsignificant trend for a lower sexual activity assessed as a dichotomic ‘yes/no’ category in the group of women with confirmed VVA, as evaluated with the DIVA-C questionnaire ($P = 0.013$),” Dr. Nappi said.

On the other hand, there was a significant association between being sexually active and the severity of particular symptoms, especially those related to intercourse, such as pain or bleeding. “Symptoms were more severe in the sexually non-active population,” she said.

Also, compared to the sexually non-active group, the group of sexually active women had a higher number of previous treatments for VVA ($P < 0.0005$) and more frequently used lubricants instead of moisturizers ($P < 0.0005$).

“I continue to be astounded by the epidemic condition of VVA among postmenopausal women, in spite of the treatments available to effectively relieve the condition, such as local estrogen therapy, prasterone or the novel oral selective estrogen receptor modulator (SERM) ospemifene,” Dr. Nappi said.

She noted that the evidence that women with more severe symptoms take specific treatments “underscores the fact that women wait too long before reaching out for help and that possibly healthcare professionals do not ask about VVA in a timely fashion.”

She believes it is important that women be treated early in the trajectory of VVA, “before the condition becomes so severe to significantly interfere with sexual function and quality of life.”

Her hope is that having better insight into VVA will help the medical community to uncover it in the office, as is the case with osteoporosis and cardiovascular risks.

DISCLOSURES Dr. Nappi reports no relevant financial disclosures.

FOR REFERENCES VISIT contemporaryobgyn.net/vvatrophyl2
Acelerated biological aging was seen in women who had severe menopausal vasomotor symptoms (VMS) on enrollment in the Women’s Health Initiative Observational Study (WHI-OS), or late-occurring VMS (at enrollment but not at during their reported menopause transition, according to a study in The Journal of Clinical Endocrinology & Metabolism.

"Previously, we discovered that VMS was associated with indicators of age-related health risks, such as cardiovascular disease (CVD) and osteoporosis," said senior author Rebecca Thurston, PhD, a professor of psychiatry, psychology and epidemiology at the University of Pittsburgh. "We were interested in finding out if women with VMS had greater underlying epigenetic aging."

The investigators examined connections between menopausal VMS and biological aging in 1,206 participants of the WHI-OS (average age 65 years at enrollment) who retained both ovaries and were not taking hormone therapy. Recruitment for baseline assessment occurred between 1993 and 1998. The sample comprised 55% non-Hispanic White women, 26% non-Hispanic Black women and 19% Hispanic women. Roughly one-third of the sample reported VMS at enrollment and 60% of the sample had VMS at some point during the menopause transition and/or at enrollment.

Connections between menopausal VMS and biological aging were assessed by two DNA methylation-based epigenetic aging indicators formerly linked to poor health outcomes: DNAm Phenome-Age and DNAm GrimAge. Although no single metric proposed to characterize biological aging is universally accepted, DNAm-based indications offer the advantage of being a broad-based marker of accelerated aging across a diverse set of bodily systems and indicate robust relationships with adverse health outcomes, including CVD, mortality and Alzheimer's disease.

The study concluded that severe hot flashes at enrollment were significantly associated with higher DNAm Phenome-Age compared to no hot flashes: odds ratio (OR) = 2.79; P = 0.028. Late-occurring VMS were also associated with a significantly higher DNAm Phenome-Age (OR = 2.15; P = 0.011), and significantly higher DNAm GrimAge (OR = 1.09; P = 0.010), relative to no VMS.

“We were not surprised that VMS were associated with greater epigenetic aging, given other findings linking them to health risks,” Dr. Thurston told Contemporary OB/GYN. “However, to my knowledge, we are the first to show this association. But we do not know at this time why postmenopausal women with severe or late-occurring VMS have greater biological aging.”

Three factors significantly associated with greater epigenetic aging for both DNA indicators were racial/ethnic minority status compared to White women (P = 0.0001), lower education (P = 0.001) and a higher body mass index (BMI) (P < 0.0001). Greater pack years of smoking was also a significant risk factor for biological aging, but only for DNAm GrimAge (P < 0.0001).

The authors accounted for these factors in their analyses, and therefore associations between VMS and epigenetic aging were not explained by them.

Based on study results, "women with VMS, particularly later in life, should engage in healthy preventive health measures,” said Dr. Thurston, president of the North American Menopause Society (NMS).

The next two steps will be to investigate women at the time of their menopause transition, as opposed to the WHI women who are considerably older, and to use more rigorous measures of VMS, such as physiologic measures of VMS and prospective, self-report measures of VMS.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

Dr. Thurston is a consultant to Astellas Pharma, Virtue Health, Pfizer and Procter & Gamble.

SOURCE
Changes in hot flashes in women with breast cancer

by BOB KRONEMYER

A study in the journal *Menopause* found that a significant proportion of premenopausal and perimenopausal women experienced hot flashes after receiving breast cancer treatment. The Taiwanese investigators said women with breast cancer who have increased body mass index (BMI) changes or those that still regularly menstruate are particularly vulnerable to them.

The percentage of Taiwanese women younger than age 50 diagnosed with breast cancer is roughly 50%, compared to only around 20% in either the United States or the United Kingdom. In addition, many Taiwanese women are still menstruating at the time of diagnosis.

The study consisted of 90 perimenopausal or premenopausal women newly diagnosed with breast cancer and scheduled to receive chemotherapy and hormonal therapy at Chang Gung Memorial Hospital in Taipei City. Mean age of participants was 43.86 years and age at menarche was 13.06 years. In total, 87.8% of women were still regularly menstruating (premenopausal) and 12.2% had irregular menstruation (perimenopausal).

Hot flash frequency and other symptoms were measured six times from prechemotherapy to 24 months after chemotherapy. Hot flash frequency was determined by an author-developed diary, in which women were asked to record every episode of a perceived daytime hot flash, and recalled nighttime hot flashes upon awakening the next morning.

The degree of hot flash interference with daily activities and overall quality of life was measured by the 10-item Hot Flash-Related Daily Interference Scale (HFRDIS), which including work, social activities, leisure activities, sleep and mood. Anxiety, depression and loss of sex were based on the Greene Climacteric Scale (GCS).

The prechemotherapy occurrence rate of hot flashes was 7.9%, which rapidly escalated to 42.5% by the end of chemotherapy, and then slightly increased to the highest rate of 46.8% at 6 months after completing chemotherapy. The frequency of hot flashes during the 24-month follow-up period following completion of chemotherapy ranged from 39.7% to 46.8%, significantly higher than baseline.

Findings

Three significant predictors of hot flash frequency were menstrual status (*P* = 0.006), loss of interest in sex (*P* = 0.013) and BMI change (*P* = 0.020). At any time point, increased BMI was associated with both higher hot flash frequency (*P* = 0.020) and hot flash interference (*P* = 0.002), while anxiety (*P* < 0.001) and loss of sexual desire (*P* = 0.038) were linked to higher hot flash interference.

The connection between loss of interest in sex and hot flashes was expected, according to the authors, because they are considered symptoms of menopause, with reduced estrogen as perhaps the common cause of both.

Six months after completing chemotherapy, premenopausal women reported significantly higher hot flash frequency than perimenopausal women (*P* = 0.041).

“...The abrupt decline of estrogen due to chemotherapy may be the cause of HFS occurring more frequently in premenopausal women than in perimenopausal women,” the authors wrote. “Indeed, the abrupt decrease in estrogen after removing the ovaries and fallopian tubes results in more severe climacteric symptoms than in natural menopause.”

Weight control and stress management programs are two strategies that may help breast cancer survivors cope with hot flashes caused by cancer treatment.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

SOURCE


**Menopausal symptoms** Read about how menopausal symptoms can be affected by seasonal variations. contemporaryobgyn.net/menopause/menopausal-symptoms-through-seasons
For patients with osteoporosis, drug treatments with bisphosphonates, particularly zoledronate, may not reduce overall mortality rates, according to a meta-analysis of 38 clinical trials of drug treatments for osteoporosis among 101,642 patients. Consequently, the authors of the analysis in JAMA Internal Medicine recommend that these medications be restricted to decreasing fracture risk.

The investigators searched Science Direct, MEDLINE, Embase and the Cochrane Library for randomized, placebo-controlled clinical trials published or in press between 2010 and April 2019; conference abstracts from annual osteoporosis society meetings were also included. Of the 2,045 records screened, only 1.8% were included in the meta-analysis. The four inclusion criteria were clinical trials that were randomized, double-blind and placebo-controlled; drug treatments with proven antifracture efficacy; agents used at the approved dose for treatment of osteoporosis; and study duration of at least 1 year. No significant connection was found between all drug treatments for osteoporosis and overall mortality rate: risk ratio (RR) = 0.95; 95% confidence interval (CI): 0.86 to 1.04. The same relationship held true for zoledronate treatment as well: RR = 0.88; 95% CI: 0.68 to 1.13. However, there was evidence for heterogeneity of the overall results: $I^2 = 48.2\%$. A prior review of a small number of clinical trials of drug treatments for osteoporosis in Osteoporosis International indicated there may be a link with increased mortality, reflecting the comorbidity and age of the participants. But the current larger analysis found “no significant association between the mortality rates in the placebo groups of the clinical trials and the association of treatment with mortality for all drug treatments,” the authors wrote. There was less certainty, though, for the association between intravenous zoledronate treatment and mortality rates because of the heterogeneous results of the clinical trials. Specifically, two large studies of zoledronate treatment found 28% and 35% reductions in mortality, respectively, which were not observed in other clinical trials.

Similarly, observational studies reported 25% to 60% reductions in total mortality rates, which were too great of a reduction to attribute to a decrease in fracture risk. “Therefore, the reduced mortality rates would likely be owing to the direct biological effects of these treatments rather than the reduced fracture risk,” the authors wrote. In addition, observational studies of patients receiving bisphosphonate therapy who had lower mortality may not have measured confounding factors that could have contributed to this lower mortality.

The apparent reduction in mortality may be the power of the placebo effect, for which the authors cite a Women’s Health Initiative study that showed that women in the placebo group who had at least 80% adherence to placebo treatment attained a 36% lower overall mortality than those with less than 80% adherence, despite adjusting for multiple potential confounding factors. The placebo effect is especially apropos for treating osteoporosis because only roughly 50% of women who take oral medications for the condition continue their regimen for 1 year, with even fewer continuing longer. The authors said additional studies are needed to elucidate whether treatment with zoledronate reduces mortality rates in patients with osteoporosis.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

SOURCE
STEVEN R. CUMMINGS, MD; LI-YUNG LUI, MA, MS; RICHARD EASTELL, MD, FRCP; ISABEL E. ALLEN, PHD.
Managing BRCA results from 23andMe

by VICTOR R. COTTON, MD, JD, AND DOUGLAS H. KIRKPATRICK, MD

During a routine office visit, a patient mentions that she recently submitted a saliva sample to 23andMe. The company performed BRCA analysis and the patient wants to discuss the results with you. How should you approach the discussion?

A generation ago, the Internet gave patients unprecedented access to medical information and thereby changed the nature of doctor-patient interaction. Rather than physicians being the sole source of medical information, patients began accessing information online and then bringing it to their physicians for discussion. The approval of 23andMe’s BRCA test changed the roles of doctor and patient yet again, as patients are now ordering genetic tests themselves and bringing the results to their physicians for interpretation. Whether this moves the doctor-patient relationship in the right direction is debatable; however, there is no debate that these test results can be clinically significant and must be handled appropriately. This article provides a foundation for doing so.

“Consumer” genetics, also known as “over-the-counter” genetics, is initiated by patients without the authorization of a clinician. It began in 2006 as an entertaining way of tracing family lineage and quickly became very popular, with more than 5 million people having submitted samples for analysis.1 In 2015, the focus expanded from recreational into clinical when 23andMe began testing for Bloom Syndrome, a rare autosomal recessive disorder of gene BLM. BRCA analysis was added in 2018, and the 23andMe panel now includes 13 genetic diseases.2 The company also offers carrier testing for autosomal recessive conditions (e.g., cystic fibrosis), which it markets to couples who are planning to have children.

Although 23andMe provides consumers with personalized information on numerous medical conditions, it does not provide one-on-one clinical interaction whereby this type of information is normally shared. Instead, consumers are notified when their results become available, and they can directly access the information online, where it is summarized in a “Genetic Health Risk Report.” To prepare consumers for the possibility of “bad news,” they are required to watch an educational video prior to accessing any result that 23andMe deems “potentially sensitive” (e.g., BRCA, Parkinson’s disease).

The absence of a one-on-one relationship with a healthcare provider is a serious shortcoming, especially for patients who learn that they harbor a pathogenic mutation by reading a report on their mobile device.4 They are often emotionally devastated and frequently turn to their physicians for guidance.

In terms of responding to these patients, it is important to first understand the nature of the test. Although 23andMe’s methodology has high levels of both accuracy (> 99% concordance with Sanger sequencing (which has been the gold standard for genetic sequencing for 40 years) and reproducibility (> 99%), the test has numerous limitations.5

First, because the saliva samples are collected in a non-clinical setting, specimen integrity could be compromised. This risk is elevated by the common practice of multiple friends or family members collecting, labelling, and submitting their specimens in the same setting.

Second, in contrast to high-end, clinical-grade labs, which always confirm pathogenic findings with Sanger sequencing before issuing a report, 23andMe’s reports are based on genotyping alone, without any confirmation. Finally, although there are more than 1000 pathogenic BRCA mutations, 23andMe tests for only the three mutations that are common in the Ashkenazi Jewish population (BRCA1 185delAG, BRCA 15382insC,
and BRCA2 6174delT). However, even among Ashkenazi Jews, this approach has limitations because they can occasionally have non-Ashkenazi mutations. So, given the numerous limitations, the US Food and Drug Administration requires 23andMe to include the following warning in its Genetic Health Risk Reports: *This test is not a substitute for visits to a healthcare provider for recommended screenings... and should not be used to determine any treatments.*

To expedite this process, the lab should be informed of the mutation that was identified and asked to confirm its presence with single-site testing. This approach is both faster and less expensive than full panel testing. In most cases, the pathogenic mutation will be confirmed and the patient can be managed accordingly.

However, on rare occasions, the pathogenic mutation will not be confirmed, and the clinician will thus be left with conflicting results: a positive from 23andMe and a negative from a clinical-grade lab. This scenario should always be resolved in favor of the clinical-grade lab. Those labs not only have higher levels of accuracy, when performing single-site testing, they always confirm both positives and negatives with Sanger sequencing. A negative result on single-site testing from a high-end lab would thus represent two negative results (one by Next-Gen sequencing and one by Sanger sequencing). Because this methodology is vastly superior to the genotyping performed by 23andMe, conflicting results should always be resolved in favor of the clinical-grade lab.

**SCENARIO 2:**
*The report is negative for a pathogenic BRCA mutation.*

While this is certainly better than a positive result, it means only that the patient most likely does not have one of the three Ashkenazi founder mutations. However, there are more than 1000 other pathogenic mutations that she could have.

In terms of responding to this patient, you should first explain the limitations of the 23andMe test and then use the discussion as an opportunity to determine whether she meets criteria for clinical-grade testing (Table 1). Between 5% and 15% of women meet criteria, 1 in 400 harbor a pathogenic mutation, and many others will be identified as being high-risk negative (i.e., they do not have a pathogenic mutation but are nonetheless at very high risk of developing cancer.) The patient’s request to discuss her 23andMe result could thus serve as a gateway to clinical-grade testing and, with it, significant changes in her management.

**SCENARIO 3:**
*The patient has not yet submitted her sample to 23andMe. She originally planned to undergo just genealogy testing (to determine her heritage), but asks if she should also have BRCA testing.*

As in Scenario 2, your response to this patient should begin by updating her personal and family history to determine if she meets criteria for clinical-grade testing. Ideally, practitioners can incorporate this “cancer” family history questionnaire (see next page for link) into their existing electronic medical record system. If this results in the patient having such testing, then there is nothing to be gained by also testing with 23andMe. Positive results can be interpreted by the practitioner and/or in conjunction with a clinical genetic counselor.

On the other hand, if the patient does not meet criteria for clinical-grade testing (and thus does not qualify for insurance coverage), then the...

National Society of Genetic Counselors: Blog “FDA Approved 23andMe At Home Genetic Tests: It’s more than just a test:” [https://www.nsgc.org/p/bl/et/blogaid=898](https://www.nsgc.org/p/bl/et/blogaid=898)

Myriad Family History Questionnaire: For use by ob/gyns as part of EMRs to identify patients and begin to offer genetic testing: [https://www.nsgc.org/p/bl/et/blogaid=898](https://www.nsgc.org/p/bl/et/blogaid=898)
tive Day 3, the patient complained of increasing pain, despite passing some flatus. Her vital signs were essentially unchanged, with a temperature of 98.2º F, BP = 145/80, pulse = 100 bpm, and respirations of 22 per minute. The peritoneal drain had 50 cc of serous drainage over 24 hours. The woman’s abdomen was soft but distended, with some sluggish bowel sounds.

Later in the morning on postoperative Day 3, the pathologist personally notified the gynecologist that the biopsy specimen was consistent with a ruptured colonic diverticulum with adjacent abscess and smooth muscle with associated colonic mucosa. A surgical consult was obtained, and an abdominal computed tomography (CT) scan revealed a partial small bowel obstruction, an amorphous 4 x 6-cm left-sided pelvic mass containing fluid and gas, with possible diverticular disease. The patient underwent surgical exploration with findings of a large, inflammatory mass encompassing the entire left side of the pelvis. There was a 1-cm hole found in the lateral portion of the sigmoid colon, as well as a residual ovarian cyst, densely adherent to the surrounding structures. Neither the left ovary nor the ovarian cyst could be excised in total; thus, the ovarian cyst was aspirated and biopsied. The surgeon performed a segmental sigmoid colectomy and created a colostomy. During a 2-month postoperative course, complications included a small bowel obstruction, with multiple surgeries. Ultimately, the colostomy was reversed months later.

The patient filed a suit against the gynecologist, alleging misdiagnosis and negligently performed surgery.

At trial, the plaintiff’s experts included a gynecologist, who opined that the preoperative work-up was incomplete and should have included a pelvic exam and a CT scan, which would have established the diagnosis of a diverticular abscess. The elevated WBC count should have alerted the gynecologist to a potential infectious process, warranting further work-up prior to surgery. Further, this expert testified that the operating gynecologist breached the standard of care by failing to properly identify the anatomic structures before excising tissue. The failure to recognize the bowel perforation and inability to remove the ovarian cyst resulted in major postoperative complications and multiple surgical procedures. The plaintiff’s surgical expert echoed this opinion, further stating that the ultrasound did not demonstrate how much colon or rectum was involved, nor the location of any potential anastomosis or colostomy, precluding an appropriate preoperative informed consent. In addition, emergent surgery was not required, with better management being the placement of a percutaneous drain and antibiotics. A general surgeon should have been consulted to establish the correct diagnosis, prior to surgical intervention. As a result of the complications and multiple surgeries, the patient is at risk for additional adhesion formation, bowel obstruction, and need for future surgery. Neither plaintiff’s expert was critical of the postoperative care.

Defense experts, including a gynecologist and general surgeon, testified that both the ED physician and the treating gynecologist thought the mass was ovarian in origin, supported by the abdominal and pelvic ultrasound. Further, the radiologist did not recommend a CT scan to further clarify the sonographic findings. The patient had no history of diverticular disease or long-term bowel-related symptoms. Thus, a diverticular abscess was unlikely. Thus, surgical consultation was not required before proceeding with surgery, which was a reasonable option in management. For further support, a defense medical expert testified that diverticular disease is uncommon in young individuals, again making the diagnosis of a diverticular abscess very unlikely. The elevated WBC could be consistent with either torsion or partial rupture of the ovarian cyst.

The defense experts testified that...
the large mass encountered at surgery was consistent with the preoperative diagnosis of an ovarian cystic mass. The markedly distorted anatomy and inability to excise the ovarian mass completely rendered aspiration and biopsy an appropriate management option. Postoperative management was appropriate, with a surgical consultation obtained in a timely manner when the pathology findings were known. It was further noted that, at surgical re-exploration, the operating surgeons were not able to remove the ovarian cyst or ovary, and therefore pursued aspiration and biopsy. Regarding the potential for future surgery due to abdominal adhesions, the defense experts testified that the patient had significant adhesions prior to the incident surgery, even requiring a prior exploratory laparotomy and extensive adhesiolysis. Thus, the patient was already at risk for future surgical procedures due to the adhesive disease.

After an 8-hour deliberation, the jury return a defense verdict.

Analysis

Ostensibly, this case appeared to be a certain victory for the plaintiff. The ultimate result, a defense verdict, underscores the importance of excellent legal representation and the critical nature of expert witness selection, not only for their credibility, but also for their ability to engage the jury.

The defendant was prepared to explain the thought process underlying the probable diagnosis, the decision for surgery, and the management decisions during the incident surgery. Further, the defendant clearly explained the sequence of findings in the postoperative period and the associated decision processes.

The plaintiff’s experts were somewhat dogmatic in their opinions, rejecting the value of ultrasound and even the probability of the preoperative diagnosis of an ovarian cyst. Further, they dismissed that there are multiple approaches to management, particularly when unexpected findings, such as extensive adhesions, are encountered. Contrasting this were the defense experts who discussed the value of various diagnostic modalities and the reasoning behind selecting specific modalities, such as ultrasound, CT, and magnetic resonance imaging. They supported the preoperative diagnosis of a large ovarian cyst. They expressed the difficult decisions one makes when encountering unexpected findings, which often lead to alternative treatment options.

The plaintiff’s experts seemed somewhat aloof and tended to “speak above the jury,” rather than at a level understood by the jury. In contrast, the defense experts were engaging and explained complex medical terms and decisions in simple terms, almost teaching the jury. As a result, the defense opinions had greater impact and influence on the jury. The defense counsel was credited for excellent preparation of all defense witnesses for trial testimony. The selection of an excellent attorney and expert witnesses definitely impact the ultimate outcome of a case.

Liletta IUS

and side effects and complications leading to discontinuation. These and future data will improve clinicians’ ability to counsel effectively and provide general expectations regarding a high-efficacy contraception option.

DISCLOSURES Dr. Creinin serves on an Advisory Board for Lupin, Merck & Co., and TherapeuticsMD and is a consultant for Danco, Estetra, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives research funding for contraceptive research from Dare, Fidelity Charitable, HRA Pharma, Medicines360, Sebela, NIH/NICHD and the Society of Family Planning.

FOR REFERENCES VISIT contemporaryobgyn.net/ius

Takeaways

1. Liletta, a levonorgestrel 52-mg intrauterine system (IUS), is FDA-approved for 6 years for contraceptive use.
2. Liletta is under study in a prospective phase 3 clinical trial aimed to extend the approved duration of the levonorgestrel 52-mg IUS and to better evaluate the potential non-contraceptive benefits or side effects of the system among a diverse US population.
3. For those who have not used a levonorgestrel 52-mg IUS previously, the 1-year amenorrhea rate of about 17% is typically reached by 9 months.
4. Seventy-five percent of Liletta users with heavy menstrual bleeding at baseline report absence of heavy menstrual bleeding by the end of the first menstrual cycle after insertion.
5. Liletta is available under HRSA 340B Drug Pricing Program for eligible institutions at a cost that is significantly lower than the maximum allowable price per 340B requirements.
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A 39-year-old G3P2012 presented to the Emergency Department (ED) with a complaint of 2 weeks of worsening low back and abdominal pain and more recent-onset nausea and vomiting. She had been seen in an urgent care center 4 days earlier with lower back pain, which was treated with naproxen. Her history included hypertension, which was well-controlled with a single medication, bilateral tubal ligation, subsequent ruptured ectopic pregnancy, and exploratory laparotomy with extensive adhesiolysis, performed for pelvic pain. The patient was afebrile, with stable vital signs. She had a tender, palpable mass extending into the lower abdomen from the pelvis. Pelvic ultrasound revealed a 14-cm left ovarian cyst with multiple septa and possible hemorrhage. A review of her records revealed a similar-sized mass on an ultrasound performed 5 years earlier. The only laboratory abnormality was an elevated white blood cell (WBC) count of 15,100 cells/µL.

Surgery was pursued on an urgent basis. A laparotomy was performed due to the size of the mass and the extensive adhesions documented on prior laparotomy. A large, cystic pelvic mass was encountered, but it could not be completely removed because of extensive, dense adhesions. Therefore, it was aspirated, returning 750 cc of serosanguinous fluid. A portion of the cyst wall was excised and sent to pathology. A peritoneal drain was placed.

On postoperative Day 1, the patient had a temperature of 99.2º F; blood pressure 162/76 mmHg; pulse 108 beats per minute (bpm), and respirations 15 per minute. Her abdomen was soft, with bowel sounds present. The peritoneal drain had a total of 115 cc of serous fluid over 24 hours, with no drainage over the most recent 8 hours. Urine output since the surgery was 1450 cc. The patient’s hemoglobin and hematocrit were stable at 9.8 g/dL and 29%, respectively, with a WBC of 12,400/µL. On postoperative Day 2, her temperature was 98.5º F, with a maximum temperature of 101º F over the past 24 hours. Her blood pressure was 144/82, with a pulse of 102 bpm. The intraperitoneal drain had 40 cc of serous drainage over 24 hours. The patient complained of increasing pain, nausea, and epigastric pain. Examination revealed a distended abdomen, with no bowel sounds identified. An abdominal x-ray revealed an ileus. A nasogastric tube was placed, offering some relief. On the morning of postoperative Day 2, the patient’s abdomen was noted to be diffusely tender, with rebound and guarding. A repeat x-ray showed a distended, fluid-filled bow.

Bowel injury missed, ovarian cyst not removed

The outcome in this case underscores the importance of excellent legal representation and scrupulous expert witness selection.
fFN testing can help...

- Keep patients out of the hospital
- Conserve critical resources
- Reduce potential COVID-19 exposure

fFN testing can help identify patients at low risk of imminent sPTB who can safely remain at home.

Ideas to Reduce PTL Triage Time

- Implement order sets to allow nursing staff to send fFN specimens to the lab immediately after collection
- Limit TVUS cervical length to positive fFN results only avoiding potential COVID-19 exposure of patients & staff
- Collect fFN specimens in the OB provider office
- Collaborate with hospitals and laboratories to perform fFN testing STAT for outpatient specimens to reduce patients sent into hospital OB triage
IMPORTANCE OF SCREENING FOR Tuberculosis Infection in the Ob/Gyn Community
Importance of Screening for Tuberculosis Infection in the OB/GYN Community

Tuberculosis (TB) is a major worldwide health problem, with approximately 10 million cases reported by the World Health Organization in 2019. TB is one of the top 10 causes of mortality worldwide and the leading cause of death from a single infectious agent. Although TB is a far less common disease in the United States compared to many other parts of the world (only 8000 reported U.S. cases in 2018), it can be particularly dangerous for pregnant women. TB is one of the leading causes of nonobstetric death worldwide in reproductive-age women. In women with active TB who are pregnant, there is a much higher risk of morbidity and mortality for both mother and baby. There have been case reports of vertical transmission, by which the infection jumps from mother to fetus. TB most often affects the pulmonary system, but some women can develop pelvic tuberculosis, which can lead to dysmenorrhea, dyspareunia, infertility, and a variety of other conditions.

Who should be screened?

Because of the low incidence of TB in the United States, community-based screening is not currently indicated. Several high-risk groups commonly seen in ob/gyn practices, however, should receive a TB screen.

The Centers for Disease Control and Prevention (CDC) has broken down TB risk into two primary categories: those who are at higher risk of initial TB infection and those who are at higher risk of transitioning from latent TB to active disease. A summary of these groups is included in Table 1. Patients who fall within either of these groups are typically recommended to receive TB testing if they have not recently been screened.

For the ob/gyn community, it is particularly important to be mindful of the risk of TB among women who are positive for human immunodeficiency virus (HIV). Regardless of whether or not they have active disease, AIDS, or are symptomatic, they should be screened for TB. It’s especially imperative to test women with a CD4 count < 200 cells/µL.

The number of high-risk patients in any individual ob/gyn practice will obviously vary, but roughly 2% to 10% of women in most practices will fall into this category.

Identifying women who are at high risk of acquiring or transitioning to active TB is fairly straightforward, requiring only a few simple questions at each visit (Are you HIV positive? Have you recently been exposed to anyone with TB? Have you ever been vaccinated for TB?) Women who respond yes to one or more of these and related questions, even if they have no apparent symptoms, should be educated about the importance of discovering the presence of latent TB. Many women with TB are unaware of the infection until it becomes an active, more serious condition, although generally it is easily treatable in latent stages.

It is unquestionably important to have a discussion about TB risk before or during pregnancy due to the possibility of maternal and fetal mortality and morbidity. These simple questions, however, can also be built into a discussion of social history any time a woman sees her ob/gyn.

What are the screening options?

Two primary methods are available to screen patients for TB. Previously, the primary screening method had been the Mantoux tuberculin skin test (TST) with purified protein derivative. This test is administered through an intradermal injection into the volar surface of the forearm to produce a transient wheal. Results need to be interpreted 48 to 72 hours after the injection. Depending on a patient’s baseline history and TB risk, a response of 5 mm or more is considered positive. Requiring patients to schedule two visits—the first for the injection and the second to assess any reaction—is one of the significant downsides to the TST.

<table>
<thead>
<tr>
<th>TABLE 1 High-risk TB subsets⁴</th>
<th>High-risk groups for transitioning from latent to active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• People who have spent time with someone who has TB</td>
<td>• People with HIV infection</td>
</tr>
<tr>
<td>• People who have recently immigrated from a country where TB is common</td>
<td>• People who became infected with TB in the last 2 years</td>
</tr>
<tr>
<td>• People who live or work in high-risk settings (i.e., correctional facilities, long-term care facilities or nursing homes, and homeless shelters)</td>
<td>• Babies and young children</td>
</tr>
<tr>
<td>• Healthcare workers who care for patients at increased risk for TB</td>
<td>• People who inject illegal drugs</td>
</tr>
<tr>
<td>• Infants, children, and adolescents exposed to adults who are at increased risk for latent TB infection or disease</td>
<td>• People who are sick with other diseases that weaken the immune system</td>
</tr>
<tr>
<td>Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.</td>
<td>• Elderly people</td>
</tr>
<tr>
<td></td>
<td>• People who were not treated correctly for TB in the past</td>
</tr>
</tbody>
</table>
Sensitivity of the TST is high, typically hovering between 95% and 98% among “clinical well” persons with previously treated TB, although false-negative results are higher among young children, patients with HIV, and other groups. Another drawback of the TST is that it is largely inaccurate in patients who have received the Bacillus Calmette-Guérin (BCG) vaccination, which is administered in most countries around the world, with the exception of the United States.\(^5\)

Because of these factors, the introduction of interferon-gamma release assay (IGRA) testing has been embraced by many as a more efficient and accurate TB screening option. IGRA testing involves a one-time blood draw that can be performed either in the hospital or at a local lab. These assays primarily reflect a CD4 immune response to antigens that are specific to the *Mycobacterium tuberculosis* (MTB) infection.\(^5\)

Currently, two commercially available IGRA tests have been approved by the U.S. Food and Drug Administration: the QuantiFERON\(^\text{®-TB Gold Plus and T-SPOT}\text{®-TB} tests. These tests both measure interferon-gamma release in response to MTB-specific antigens. Unlike the TST, IGRA tests are evaluated in the clinical laboratory. Test results will either come back positive, negative, or indeterminate and are typically available within a week and often sooner. In patients with an indeterminate result, a follow-up TST or second IGRA test is usually warranted.

In almost all cases, the CDC recommends IGRA testing instead of TST in patients who are age 5 years or older, although guidelines note that a TST is an acceptable alternative, especially in situations in which an IGRA is not available or is too costly or burdensome. Due to the difficulty of obtaining a blood draw in young children, TST is recommended over IGRA testing in children younger than age 5 years (the American Academy of Pediatrics suggests IGRA testing as an option starting at age 2).\(^5\,^6\) Advantages of IGRA testing include the need for only a single patient visit (results can be communicated via email or over the phone, with follow-up for any positive or indeterminate result), interpretation of results in an objective fashion, and the viability of the test in individuals who have received BCG vaccination.

### In case of a positive result

Here is perhaps the most common scenario for the practicing ob/gyn: An asymptomatic, nonpregnant woman comes in for a routine visit and it is determined that, for whatever reason, she should be screened for TB. The test comes back positive. She then undergoes a chest X-ray, which shows suspicious lesions, confirming the diagnosis.

The CDC updated their TB treatment guidelines in February 2020, offering three preferred and two alternate regimens for the treatment of latent TB that is presumed to be susceptible to isoniazid or rifampin (Table 2). These regimens include use of isoniazid and rifampin individually, as well as in combination, for a duration of 3 to 9 months. Because approximately 5% to 10% of patients with latent TB will transition to the active form of the disease during their lifetime, providers should stress the importance of treatment that can prevent this progression.\(^9\)

### TABLE 2 Recommended regimens for the treatment of latent TB\(^1\)

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Target population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Three months of weekly isoniazid plus rifapentine</td>
<td>• Adults and children aged &gt; 2 years, including HIV-positive persons as drug interactions allow</td>
</tr>
<tr>
<td>• Four months of daily rifapentine</td>
<td>• HIV-negative adults and children of all ages</td>
</tr>
<tr>
<td>• Three months of daily isoniazid plus rifapentine</td>
<td>• Adults and children of all ages, including HIV-positive persons as drug interactions allow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative regimens</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Six months of daily isoniazid</td>
<td>• HIV-negative adults and children of all ages; conditionally recommended for HIV-positive adults and children of all ages</td>
</tr>
<tr>
<td>• Nine months of daily isoniazid</td>
<td>• Conditionally recommended for adults and children of all ages, both HIV negative and HIV positive</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

In women who are pregnant, isoniazid daily or twice weekly for a duration of 9 months with pyridoxine (vitamin B6) supplementation is considered a safe and effective regimen. These agents are believed to cross the placental barriers but do not appear to have harmful effects on the fetus, and any risks are outweighed by the benefits of treatment. Women being treated with first-line antituberculosis drugs can still breastfeed, because the concentrations of these drugs in breast milk are too small to produce toxicity in the nursing newborn.\(^2\)

The treatment of active TB, of course, is much more involved for any patient and typically involves a multidrug regimen administered for 6 to 9 months. Except in rare cases in which the ob/gyn has experience and deep knowledge of the treatment of active TB, a referral to an infectious disease specialist is the most prudent course of action.

### Conclusion

Although uncommon in the United States, TB should be an important consideration for ob/gyns, especially when dealing with patients who fall within the category of high risk. Because of its high rate of morbidity and mortality when progressing to active disease, screening and appropriate treatment of any woman who tests positive for the infection is paramount.
The performance of the USA format of the QFT-Plus test has not been extensively evaluated with specimens from pregnant women.

References


