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Perimenopausal abnormal uterine bleeding

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Drug duo boosts survival rate in advanced endometrial cancer

WELL WOMAN
COVID-19 Vaccine FAQ

PRACTICAL CARE APPROACH FOR A CHRONIC CONDITION

by SARAH J. KILPATRICK, MD, PHD; AND NIRUPAMA BONTHALA, MD

ContemporaryOBGYN.net
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Few cases (0.36%) of adverse reactions of cystitis, pyelonephritis and other upper urinary tract infection (UTI) have been reported in Phexxi® clinical studies. Of these, one case of pyelonephritis was considered serious and required hospitalization. Avoid use of Phexxi® in females of reproductive potential with a history of recurrent urinary tract infection or urinary tract abnormalities.

ADVERSE REACTIONS

Most common adverse reactions were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection, vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain. 9.8% of male partners reported local discomfort.

Patients should be counseled on the following:
- To contact and consult with their healthcare provider for severe or prolonged genital irritation or if experiencing urinary tract symptoms.
- To discontinue Phexxi® if they develop a local hypersensitivity reaction.
- That Phexxi® does not protect against HIV infection or other sexually transmitted infections.
- To avoid Phexxi® use with vaginal rings.
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• That Phexxi® does not protect against HIV infection or other sexually transmitted infections.
• To avoid Phexxi® use with vaginal rings.

To report SUSPECTED ADVERSE REACTIONS, contact Evofem at toll-free phone 1-833-EVFMBIO or you may contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

INDICATIONS AND USAGE

Phexxi® (lactic acid, citric acid, and potassium bitartrate) vaginal gel 1.8%, 1%, 0.4% is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

LIMITATIONS OF USE

Phexxi® is not effective for the prevention of pregnancy when administered after intercourse. Please see full Prescribing Information for Phexxi®.

Please see Brief Summary on the following page.
The most common adverse reactions (≥2% of Subjects Who Used PHEXXI to Prevent Pregnancy) (Studies 1 and 2 – U.S. population only)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PHEXXI (N=2480) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal Burning Sensation</td>
<td>18.0</td>
</tr>
<tr>
<td>Vulvovaginal Pruritus</td>
<td>14.5</td>
</tr>
<tr>
<td>Vulvovaginal Mycotic Infection*</td>
<td>9.1</td>
</tr>
<tr>
<td>Urinary Tract Infection†</td>
<td>9.0</td>
</tr>
<tr>
<td>Vulvovaginal Discomfort</td>
<td>9.0</td>
</tr>
<tr>
<td>Bacterial Vaginosis</td>
<td>8.4</td>
</tr>
<tr>
<td>Vaginal Discharge</td>
<td>5.5</td>
</tr>
<tr>
<td>Genital Discomfort</td>
<td>4.1</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3.1</td>
</tr>
<tr>
<td>Vulvovaginal pain</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Among subjects who used PHEXXI in Studies 1 and 2, 1.6% discontinued from the clinical trials due to an adverse reaction. The most common adverse reactions leading to study discontinuation were vulvovaginal burning sensation (0.7%); and vulvovaginal pruritus and vulvovaginal discomfort (0.1% each).

Adverse Reactions in Male Partners:
Among male partners of subjects who used PHEXXI for contraception in Study 2, 9.8% (131 of 1330) reported symptoms of local discomfort (burning, itching, pain, and “other”). Of these local discomfort symptoms, 74.7% were mild, 21.4% were moderate, and 3.9% were severe. Two subjects discontinued participation in the study due to male partner symptoms.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There is no use for PHEXXI in pregnancy; therefore, discontinue PHEXXI during pregnancy. There are no data with the use of PHEXXI in pregnant women or animals. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Lactation

Risk Summary

There are no data on the presence of lactic acid, citric acid, and potassium bitartrate or their metabolites in the milk of breastfeeding females. There is no use for PHEXXI in breastfeeding females. The effects on milk production are not known.

Pediatric Use

The safety and effectiveness of PHEXXI have been established in females of reproductive potential. Efficacy is expected to be the same for post-menarchial females under the age of 17 as for users 17 years and older. The use of PHEXXI before menarche is not indicated.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Advise the patient to read the Patient Information and FDA-approved patient labeling (Instructions for Use).

Advise the patient:

- To intravaginally administer the contents of one pre-filled single-dose applicator of PHEXXI before each episode of vaginal intercourse and to administer an additional dose if intercourse does not occur within one hour of administration [see Dosage and Administration (2.1) of PHEXXI Full Prescribing Information].
- To consult their healthcare provider for severe or prolonged genital irritation [see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information].
- To discontinue PHEXXI if they develop a local hypersensitivity reaction [see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information].
- To contact their health care provider if experiencing urinary tract symptoms [see Warnings and Precautions (5.1) of PHEXXI Full Prescribing Information].
- That PHEXXI does not protect against HIV infection and other sexually transmitted infections.
I nauguration Day now has passed and we are settling in to a new year and new administration with hopes that 2021 will bring needed relief from the coronavirus disease 2019 (COVID-19) pandemic. The relief only will come with time, though the weariness may take much longer to mitigate than any virus.

In her column this month, Editor in Chief Catherine Y. Spong, MD, gives her view and reminds us not to let down our guard, just yet. “We are constantly needing to remind ourselves and others to distance in breakrooms, not eat together, and remain vigilant,” she writes. “We now have the vaccine, rolled out in different strategies in each state, yet the uptake is not as robust as hoped. Vaccine roll-out has been challenging, with facilities wanting to protect the most vulnerable and ensure it is performed with the requisite so-cial distancing.”

During a press conference on January 14, 2021, the Infectious Disease Society of America (IDSA) discussed the poor rollout of the vaccine, with one expert comparing it to trying to fill a lake with a water hose. As logistics remain a challenge, it is even more important to remind your patients to continue masking, handwashing, and social distancing.

While Americans wait, health care professionals are vetting questions from patients and others. Emily Adhikari, MD, addresses many of those questions in a COVID-19 FAQ we have included as a tear-out in this issue.

What questions are you hearing from patients or others? Let us know by contacting us at COGeditorial@mmhgroup.com.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
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CONTEMPORARY OB/GYN® (Print ISSN#0090-3159, Digital ISSN#2150-6264), is published monthly by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512-0457. One-year subscription rates: $135.00 per year (USA and Possessions); $159.00 per year (outside USA). Single copies (presale only): $30.00 in the USA; $32.00 per copy worldwide. Includes $6.00 per order plus $2.00 for US postage and handling. Periodicals postage paid at Trenton, NJ 08638 and additional mailing offices.

POSTMASTER: Please send address changes to Contemporary OB/GYN®, PO Box 457, Cranbury NJ 08512-0457. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Printed in USA. Subscription inquiries/address changes: toll-free 888-527-7008, or dial direct 218-740-6477.

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We are nearing completion of 365 days of unprecedented chaos, at least for me. Although experts in infectious disease have been thinking about and planning for an infectious disease outbreak of such magnitude, many—myself included—had no expectation of it in our lifetime. Measures to stall the spread of coronavirus disease 2019 (COVID-19) and the ensuing social isolation have transformed the workplace, school, and home environments.

The availability of a COVID-19 vaccine has been touted as the start of the return to normal. Once the population is vaccinated and immunity is prevalent, we can anticipate life returning to something closer to what we once knew. That said, I recognize that the definition of “normal” will be different than how I would have described it a year ago.

The number of COVID-19 cases continues to increase (Figure), in part due to recent holiday gatherings; new, more contagious strains of the COVID-19 virus; and exhaustion with social distancing. The strain of needing to continue isolation, wear masks, be diligent about hygiene has taken a toll. We must continually remind ourselves and others to stay socially distant in break rooms, not eat together, and remain vigilant.

The vaccine now has been rolled out via different strategies in each state, yet the uptake is not as robust as hoped. Vaccine rollout has been challenging, with facilities wanting to protect the most vulnerable and ensure it is performed with the requisite social distancing. As we move to encourage vaccination, with the hope that this will stall spread, numerous questions and concerns are raised about the vaccine. Importantly, these concerns are not just among the lay public—many providers and hospital personnel also have questions and concerns. If health care workers, who clearly have seen the devastation of this virus, are not willing to accept vaccination, it will be difficult to sway the lay public.

Many of the concerns swirl on social media: “Will the vaccine impact fertil-
ity, hair growth or loss, or onset of Bell’s palsy?” Some have a grounding in the trials that led to the vaccine’s approval, and others seemingly appear without any basis in fact. In this issue of Contemporary OB/GYN, Emily Adhikari, MD, medical director of Perinatal Infectious Diseases at Parkland Health and Hospital System and an assistant professor of obstetrics and gynecology at the University of Texas Southwestern Medical Center in Dallas, addresses these frequently asked questions. She has created a tear-out for our Well Woman section on Page 15, also available for download online, for your practice guidance.

We all need to understand the facts about vaccination; be role models of hygiene, masking, and social distancing; and talk with our coworkers, practitioners, family, and friends to address their questions about vaccination.

I sometimes wonder if I am having a nightmare and will wake up to find all is well with the world, only to realize that it is all too true. Recognizing that others, less informed than we are, also may be experiencing the same thoughts means that we must continue to offer hope and encouragement to our coworkers, patients, friends, and communities. Please stay strong and stand tall.

Catherine Y. Spong

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. Email her at cspong@mjhlifesciences.com

FOR REFERENCES VISIT contemporaryobgyn.net/normal2021

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?

Email Dr. Spong at CSpong@mjhlifesciences.com

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COVID-19 Vaccine: Questions and answers for practicing ob/gyns and their patients

Senior Editor Angie DeRosa recently interviewed Emily Adhikari, MD, Medical Director of Perinatal Infectious Diseases at Parkland Hospital and an assistant professor of Obstetrics and Gynecology in the division of maternal-fetal medicine at the University of Texas Southwestern Medical Center in Dallas. During the interview, Adhikari dispelled many myths surrounding the vaccine’s efficacy, safety, side effects, and more.

Watch the full interview online at: contemporaryobgyn.net/AdhikariQA
BOOK REVIEW

Protocols for High-Risk Pregnancies, 7th Edition

Snapshot: Protocol 11 - Maternal Anemia

Definition
During a singleton gestation, plasma volume doubles (increasing approximately 1000 mL) and red blood cell (RBC) volume increases by 25% (300 mL), with RBC production slightly behind plasma expansion. This results in a physiologic dilutional anemia of pregnancy, which reaches a nadir during the late second to early third trimester (Table 1). The Centers for Disease Control and Prevention defines anemia as a hemoglobin (Hb) below the fifth centile for a healthy, iron-supplemented population. This translates to a threshold of Hb less than 11 g/dL in the first and third trimesters and less than 10.5 g/dL during the second trimester. Rates of anemia in pregnancy vary widely between different populations and socioeconomic classes.

Consequences
In developed countries, maternal anemia has been associated with increased risk of preterm birth and low birth weight infants, as well as neonatal and perinatal death. In addition, maternal complications associated with anemia include preeclampsia, cesarean delivery, postpartum depression, and an increased likelihood for transfusion, either intrapartum or postpartum, despite equivalent blood loss. Women with anemia are asymptomatic or describe vague symptoms such as fatigue and palpitations; therefore, screening for anemia during pregnancy is recommended regardless of symptoms.

Diagnostic Work-up and Treatment
Causes of anemia may be classified by pathophysiology, such as comparing acquired versus inherited causes or mechanisms of anemia such as decreased RBC production versus inherited causes.

AUTHOR: Elaine Duryea, MD is an assistant professor in the Department of Obstetrics and Gynecology at UT Southwestern Medical Center and medical director of the Maternal-Fetal Medicine Clinic at Parkland Health and Hospital System.

SYNOPSIS: A comprehensive review of all causes of anemia may be intimidating, and many available algorithms are not high yield when evaluating pregnant women. The protocol presented provides an algorithm for the initial evaluation of anemia in pregnancy, with treatment algorithms for the most common causes in pregnancy. Women who do not meet one of the definitions provided below are best managed in consultation with a hematologist.

Read the complete chapter now. contemporaryobgyn.net/MatAnemiaCH

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creased destruction. In clinical practice, more often the evaluation of maternal anemia starts with the mean corpuscular volume, based on which anemias are defined as microcytic (<80 fL), normocytic (80-100 fL), or macrocytic (>100 fL; Figure 1).

**Macrocytic Anemia**

Figure 1 shows the appropriate work-up for the search of causes in the presence of macrocytic anemia.

**VITAMIN B₁₂ DEFICIENCY** is rare, as most healthy individuals have 2 to 3 years' storage available in the liver. However, vitamin B₁₂ deficiency can be encountered in individuals who have undergone bariatric surgery with partial gastric resection and are noncompliant with recommended vitamin B₁₂ supplementation (350 µg/day sublingually plus 1000 µg intramuscular every 3 months if needed), in individuals with pernicious anemia (an extremely uncommon autoimmune disease in women of reproductive age that is diagnosed by the presence of serum intrinsic factor antibodies), and in individuals with malabsorption (eg, Crohn disease or ileal resection).

**FOLATE DEFICIENCY** is less common today given the supplementation of foods with folate and universal folic acid supplementation in pregnancy. Recommended folate requirements are 400 µg/day during pregnancy, with higher doses recommended in the presence of multiple gestations, with hemolytic disorders such as sickle cell anemia or thalassemia, and in patients taking antiepileptic drugs or sulfa drugs (eg, sulfasalazine). In addition to macrocytic anemia, folate deficiency may also cause thrombocytopenia.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Changes in Laboratory Values in Pregnancya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonpregnant women</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12-16</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>36-46%</td>
</tr>
<tr>
<td>RBC count (× 10⁶/mL)</td>
<td>4.8</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>80-100</td>
</tr>
<tr>
<td>MCHC</td>
<td>31%-36%</td>
</tr>
<tr>
<td>Reticulocytes (× 10⁹/L)</td>
<td>50-150</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>RDW</td>
<td>11%-15%</td>
</tr>
</tbody>
</table>

MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width.

*Adapted from ACOG Practice Bulletin No. 107, 2009, with permission from Lippincott Williams & Wilkins.

If a diagnosis of folate deficiency is made or the woman had a prior pregnancy affected by a neural tube defect, the recommended dose of folic acid is 4 mg/day. Anemia due to folate or B₁₂ deficiency should respond briskly, with an elevated reticulocyte count, within 4 to 7 days of beginning treatment. In the case of macrocytic anemia with normal folate and vitamin B₁₂ levels, a consultation with a hematologist is indicated for bone marrow biopsy.

**Normocytic Anemia**

The recommended laboratory evaluation for normocytic anemia is displayed in Figure 2. A high reticulocyte count indicates either hemolysis or blood loss with resultant bone marrow activation. If a normocytic anemia with an elevated reticulocyte count is

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Oral Preparations for Therapy of Iron Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of iron</td>
<td>Elemental iron (mg)</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>64-200</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>38</td>
</tr>
<tr>
<td>Ferric</td>
<td>50-150</td>
</tr>
</tbody>
</table>

*Adapted from ACOG Practice Bulletin No. 107, 2009, with permission from Lippincott Williams & Wilkins.
found, a careful history and evaluation of laboratory studies for hemolysis, such as Coombs test, peripheral smear, and lactate dehydrogenase level, are recommended. A normal or low reticulocyte count in the setting of anemia raises concern for iron deficiency (a ferritin level < 10-15 μg/dL is diagnostic) or bone marrow suppression/disorders. Low reticulocyte count with normal or high serum ferritin levels can be seen in the presence of hypothyroidism or chronic disorders, such as inflammatory bowel disease, systemic lupus erythematosus, granulomatous infections, malignant neoplasms, and rheumatoid arthritis. Hematology consultation for further assessment is indicated in these circumstances.

Mixed nutritional deficiencies (folate and iron) may lead to normocytic anemia in pregnancy, but routine supplementation makes the probability of such a scenario low. If concern for a mixed nutritional deficiency does arise, the red cell distribution width (RDW), a marker of increased variability in red cell size or anisocytosis, is a useful indicator because an RDW greater than 15% indicates the presence of nutritional deficiencies.

**Microcytic Anemia**

Most cases of microcytic anemia in pregnancy are due to iron deficiency anemia. Evaluation of a ferritin level should be the next step in evaluation. Serum ferritin is the most sensitive and specific screening test for iron deficiency (with < 10-15 μg/dL indicating depleted iron stores). If serum ferritin is normal or high, the next step is hemoglobin electrophoresis to evaluate for a thalassemia. Such situations usually warrant consultation with a hematologist for further evaluation and bone marrow biopsy as indicated.

**Iron Supplementation in Pregnancy**

In a typical singleton gestation, maternal iron requirements (including blood volume expansion as well as fetal and placental requirements) average 1 g for the entire pregnancy, with this requirement further increased in the setting of multiple gestations. In a landmark study of healthy, nonanemic, menstruating young women who agreed to bone marrow biopsy, 66% had inadequate iron stores. For the above reasons, and because gastrointestinal adverse effects (AEs) of oral iron supplementation (constipation, nausea, and diarrhea) are negligible with doses less than 45 to 60 mg, supplementation with elemental iron (30 mg/day) is recommended for all pregnant women in the United States, regardless of indices. Supplementation should be continued until 3 months postpartum in areas with high prevalence of anemia.

A review of randomized clinical trials (most performed in Western countries) shows that routine supplementation in nonanemic women results in higher maternal Hb levels at term and 1-month postpartum, higher serum ferritin levels, lower rates of anemia at term (relative risk [RR] = 0.26) and of iron deficiency anemia in particular (RR = 0.33), and higher serum ferritin levels in the infants. However, no differences are noted in most clinical outcomes (such as preterm birth, pre eclampsia, or need for transfusion), birth weight, small for gestational age, perinatal mortality, or need for admissions to neonatal intensive care unit.

**Treatment of Iron Deficiency Anemia**

Compared with routine supplementation in pregnancy, higher doses of iron are required for the treatment of maternal anemia (up to 200 mg/day).

**ORAL IRON** therapy is most often utilized, with a list of the most commonly available formulations in Table 2. Enteric-coated forms should be avoided because they are poorly absorbed. Absorption is increased by intake of iron on an empty stomach and with vitamin C or orange juice. Although several trials have been conducted to compare iron formulations, it is not...
possible to assess the efficacy of the treatments due to the use of different drugs, doses, and routes. Gut absorption decreases with increasing doses of iron; therefore, it is best to divide the total daily dose into 2 or 3 doses. A relationship is present between dose of oral iron and gastrointestinal AEs, with worsening of symptoms as dose increases, with such AEs leading to discontinuation of therapy in 50% of women. To encourage adherence, it is important to minimize AEs by increasing the dose gradually, with larger doses in the evening, and considering the use of an iron sulfate elixir, which allows more gradual titration of dose. Stool softeners are often required to prevent constipation. Serum reticulocyte count should be elevated within 7 to 10 days of treatment initiation, with a slower improvement in Hb levels. Expect Hb deficit to halve in 1 month and normalize 6 to 8 weeks after initiation of treatment. To replenish iron stores, oral therapy should be continued for 3 months after the anemia has been corrected.

**INTRAVENOUS (IV) IRON** therapy is generally reserved for women who cannot or will not take oral iron preparations. Hb indices are equivalent after 40 days of treatment in women receiving IV iron therapy as compared to those receiving oral therapy, but the rate of rise is more rapid in women receiving IV therapy. Randomized trials have not shown significant differences between the 2 forms of supplementation in need for maternal blood transfusion, in neonatal birth weight, or in neonatal anemia, and findings have demonstrated a preference for oral supplementation among most women. Therefore, IV therapy is indicated only in patients with severe anemia with intolerance to oral therapy or malabsorption. Iron dextran is associated with a greater risk of anaphylaxis and is not recommended in light of other available formulations with a lower risk of allergic reaction.

**ERYTHROPOIETIN** is not indicated in the treatment of iron deficiency anemia unless the anemia is caused by chronic renal failure or other serious chronic medical conditions; it is expensive, with many associated AEs, so its use should be reserved for treatment by a hematologist.

**BLOOD TRANSFUSION** is indicated only for anemia associated with hypovolemia from blood loss or in preparation for a cesarean delivery in the presence of severe anemia.

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**FOR REFERENCES VISIT** contemproaryobgyn.net/MatAnemia

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**Figure 2. Algorithm for Evaluation of Normocytic Anemia**

- **HIGH**
  - Reticulocyte count
  - Hemolysis or blood loss

- **LOW**
  - Ferritin
  - History, hemolysis labs if indicated (Coombs test, peripheral smear)

**Figure 3. Algorithm for Evaluation of Microcytic Anemia**

- **LOW**
  - Serum ferritin
  - Iron deficiency

- **NORMAL OR HIGH**
  - Hemoglobin electrophoresis
  - History, hemolysis labs if indicated (Coombs test, peripheral smear)

- **HIGH**
  - HbA2 & F
  - DNA probe for alpha thalassemia

- **FREE**
  - Free erythrocyte protoporphyrin

- **BONE MARROW BIOPSY**

HbA2, hemoglobin A2; HbF, hemoglobin F.
IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.
• Females over 35 years old who smoke should not use ANNOVERA.
• Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use.

CONTRAINDICATIONS

ANNOVERA (segesterone acetate and ethinyl estradiol vaginal system) is contraindicated and should not be used in women with a high risk of arterial or venous thrombotic diseases; current or history of breast cancer or other estrogen- or progestin-sensitive cancer; liver tumors, acute hepatitis, or severe (decompensated) cirrhosis; undiagnosed abnormal uterine bleeding; hypersensitivity to any of the components of ANNOVERA; and use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

WARNINGS AND PRECAUTIONS

• Stop ANNOVERA if a thrombotic or thromboembolic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Start ANNOVERA no earlier than 4 weeks after delivery, in females who are not breastfeeding. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years.
• Discontinue if jaundice occurs.
• Stop ANNOVERA prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir: ANNOVERA can be restarted 2 weeks following completion of this regimen.
• Do not prescribe ANNOVERA for females with uncontrolled hypertension or hypertension with vascular disease. Monitor blood pressure and stop use if blood pressure rises significantly in females with well-controlled hypertension.
• Monitor glucose in pre-diabetic or diabetic females taking ANNOVERA. Consider an alternate contraceptive method for females with uncontrolled dyslipidemias.
• Patients using ANNOVERA who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated. ANNOVERA should be discontinued if indicated.
• Other warnings include: gallbladder disease; depression; cervical cancer; increased serum concentrations of binding globulins; hereditary angioedema; chloasma (females who tend...
Combination containing ombitasvir/paritaprevir/ritonavir, components of ANNOVERA; and use of Hepatitis C drug

CONTRAINDICATIONS

IMPORTANT SAFETY INFORMATION

• Cigarette smoking increases the risk of serious
• Females over 35 years old who smoke should not use ANNOVERA.

WARNING: CIGARETTE SMOKING AND SERIOUS

CONTRACEPTIVE USE.

ReDefine Long-Term Contraception

The only hormonal birth control with a predictable bleeding profile

1,2*† Empower her to be in

high patient satisfaction:

97.3% effective

and

5-10% of females experienced unscheduled bleeding and/or spotting for ~1 day or less per 28-day cycle.

CARDIOVASCULAR EVENTS

Results based on data from 905 subjects in the areas of ease-of-use, expulsion, side effects, and sex/intercourse.

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of ANNOVERA or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with ANNOVERA.

INDICATION

ANNOVERA is a progestin/estrogen combination hormonal contraceptive indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use: ANNOVERA has not been adequately studied in females with a body mass index >29 kg/m².

Please note this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information on the next page, including BOXED WARNING, or visit Annovera.com/pi.pdf.

ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system)  

BRIEF SUMMARY OF PRESCRIBING INFORMATION  

This Brief Summary does not include all the information needed to use ANNOVERA safely and effectively. Please read the ANNOVERA.com/pi.pdf for Full Prescribing Information (Ph).  

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS  

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use. This risk increases with age, particularly in females over 35 years of age, and with the duration of smoking. For this reason, CHCs should not be used by females who are over 35 years of age and smoke.  

INDICATIONS AND USAGE  

ANNOVERA is indicated for use by females of reproductive age.  

ANNOVERA is contraindicated in females with a BMI >29 kg/m2.  

DOSE AND ADMINISTRATION  

Observe ANNOVERA in the vagina. The vaginal system must remain in place continuously for 23 days (21 days) followed by a 1-week (7-day) vaginal system-free interval. Once the ANNOVERA system provides contraception for twenty 7-day cycles (1 year). Follow instructions for starting ANNOVERA, including switching from other contraceptive methods, and use of backup contraception, if childbearing (see How to Start ANNOVERA (2.2) in PI).  

Contraceptive efficacy of ANNOVERA may be reduced if women use ANNOVERA out of the vagina for more than 2 continuous hours or more than 2 cumulative hours during the 21 days of continuous use, then بها’s female contraceptive contraceptions should not be used if the female contraceptive system has been in the vagina for 7 consecutive days.  

CONTRAINdicATIONS  

ANNOVERA is contraindicated in females who are known to have the following conditions:  

• A high risk of arterial or venous thrombolic diseases. Examples include females who are known to: smoke, if over age 35, have current or history of deep vein thrombosis or pulmonary embolism; have cerebrovascular disease, have coronary artery disease; have thrombogenic or rheumatic disease of the heart (for example, subacute bacterial endocarditis with valvular damage, or atrial fibrillation); have inherited or acquired hypercoagulopathies; have uncontrolled hypertension or hypertension with vascular disease; have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease, or other end-organ damage; diabetes mellitus of >20 years duration; have headaches with focal neurological symptoms, migraine headaches with aura, that do not contraindicate CHC use in younger females, are contraindicated to use. Male condoms or spermicides should be used instead.  

• Thromboembolic Disorders and Other Vascular Conditions  

Females are at increased risk for a venous thrombotic event (VTE) when using ANNOVERA. Stop ANNOVERA if a thrombotic or thromboembolic event occurs or if ANNOVERA is lost during use, especially during the first week of use. If a venous thrombotic event occurs, particularly in females over age 35 years, ANNOVERA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are taking ANNOVERA.  

• Hypersensitivity to any of the components of ANNOVERA. Hypersensitivity reactions reported include: throat constriction, facial edema, urticaria, angioedema, anaphylaxis, and/or shock. Use of Hepatitis C drugs combinations containing ombitasvir/paritaprevir/ritonavir with or without dasabuvir; ANNOVERA can be restarted 2 weeks following discontinuation of treatment if the Hepatitis C combination drug combination has been completed as prescribed.  

• Cervical Cancer  

ANNOVERA is contraindicated in females over age 35, who have a history of cervical cancer or cervical precancerous lesions. Malignancies of the cervix may be at an increased risk of cervical cancer.  

Adverse reactions leading to discontinuation by ≥1% of subjects are:  

• Depression  

Carefully observe females with a history of depression and carefully observe ANNOVERA use if depression recurs to a serious degree.  

• Migraine  

Consider alternative contraception for females with uncontrolled migraine. ANNOVERA may also be discontinued if migraine increases in intensity or frequency.  

• Metrorrhagia/menstrual disorder  

7.5% of subjects discontinued ANNOVERA use due to menstrual disorders including metrorrhagia/menstrual disorders. Metrorrhagia/menstrual disorders may be due to the potential for an increase in the risk of CHC-related hemorrhage.  

• Allergic reactions leading to discontinuation  

Most common adverse reactions include:  

• Headache  

If a patient exhibits signs/symptoms of TSS, consider the possibility of this diagnosis, remove ANNOVERA, and initiate appropriate medical evaluation and treatment.  

• Vaginal irritation  

Some females are aware of the vaginal system on occasion during the 21 days of use or during coitus, and partners may feel the ANNOVERA system during coitus. ANNOVERA may cause irritation in females with conditions that makes the vagina more susceptible to vaginal irritation or ulceration, vaginal and cervical erosion and/or ulceration has been reported in females using other contraceptive devices. In some cases, the ring adhered to vaginal tissue, which necessitated removal by a healthcare provider.  

ADVERSE REACTIONS  

Clinical Trial Experience  

Most common adverse reactions are reported in by ≥5% of ANNOVERA-treated subjects include: headache, including migraine (38.6%); nausea/vomiting (25.0%); vasovagal syncope; hypotension/collapse/vasovagal events (16.5%); abdominal pain/upper (13.3%); dysmenorrhea (12.5%); vaginal discharge (11.8%); UTI/cystitis/pyelonephritis/genitourinary tract infection (10.7%); breast/breast tenderness (9.7%); mood changes (9.7%); hot flashes (8.9%); anorexia (7.5%); fatigue (7.2%); and weight loss (5.5%).  

Adverse reactions leading to discontinuation among subjects using ANNOVERA for contraception, 12% discontinued from the clinical trials due to an adverse reaction. In addition, 1.4% of subjects discontinued ANNOVERA due to clinical trial system expulsions.  

Serious Adverse Reactions  

Serious adverse reactions occurring in ≥2 subjects were: VTEs (deep venous thrombosis, cerebral vein thrombosis, pulmonary embolism), drug hyperglycemia reactions and spontaneous abortions.  

DRUG INTERACTIONS  

Drugs or herbal products that can induce certain enzymes, including CYP3A4, may decrease the effectiveness of ANNOVERA or increase breakthrough bleeding. Counsel patients to avoid using the combination drug combinations containing ombitasvir/paritaprevir/ritonavir with or without dasabuvir, due to potential for CHC interactions.  

USE IN SPECIFIC POPULATIONS  

Pregnancy  

Discontinue ANNOVERA if pregnancy occurs.  

Lactation  

Not recommended for nursing mothers; can decrease milk production.  

Pediatric Use  

Safely and efficacy of ANNOVERA have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of ANNOVERA before menarche is not indicated.  

Geriatric Use  

ANNOVERA has not been studied in females who have reached menopause and is not indicated in this population.  

Hepatic Impairment  

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of ANNOVERA. Acute or chronic liver disease, or at least 1.4% of subjects discontinued ANNOVERA use due to hepatic impairment.  

Renal Impairment  

No studies were conducted in subjects with renal impairment; ANNOVERA is not recommended in patients with renal impairment.  

Body Mass Index (BMI)/Body Weight  

The safety and efficacy of ANNOVERA in females with a BMI >29 kg/m2 have not been adequately evaluated because this subgroup was excluded from the clinical trials after 2 VTEs occurred in females with a BMI >29 kg/m2. Dosage in females with a BMI >29 kg/m2 is associated with lower systemic exposure of SA and EE.  

Manufactured for: TherapeuticsMD, Inc.  

Boca Raton, FL 33431  

Based on MDA-LAB-20002 01/2020  

MDA-2019-5.3 02/2020
COVID-19 VACCINES

by EMILY ADHIKARI, MD

CURRENTLY, the two available vaccines for coronavirus disease 2019 are messenger RNA (mRNA) vaccines. This type of vaccine teaches cells how to make a protein, starting an immune response that creates antibodies. The antibodies protect us from getting infected when exposed to COVID-19.

The COVID-19 vaccine is different than influenza, or other vaccines, that rely on either live or inactivated virus to create the immune response.

There are two vaccines approved by the FDA. Both were tested to prevent COVID-19 disease.¹²

<table>
<thead>
<tr>
<th></th>
<th>Pfizer vaccine (BNT162b2)</th>
<th>Moderna vaccine (mRNA-1273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved age groups</td>
<td>&gt;16 years</td>
<td>&gt;18 years</td>
</tr>
<tr>
<td>Timing of 2nd dose</td>
<td>3 weeks (19-23 day range)</td>
<td>1 month (28 day)</td>
</tr>
<tr>
<td>Efficacy after 2nd dose</td>
<td>95% (90-97%); after 1-2 weeks</td>
<td>94.1%; after 2 weeks</td>
</tr>
</tbody>
</table>

Pregnancy & Lactation

- There is no evidence suggesting risk from mRNA vaccines in pregnant or lactating women, but long-term safety and efficacy studies have not yet been published. That said, there is no biologically plausible evidence to suggest that harm to a pregnant woman or her fetus is possible from these vaccines. The currently available COVID-19 vaccines contain a piece of RNA delivered within a lipid capsule. This capsule fuses with the cell membrane to deliver the mRNA. This mRNA sends a message to the cell to trigger the immune response and then is quickly degraded, never entering the nucleus or changing DNA in any way.

- According to the American College of Obstetricians and Gynecologists (ACOG), the COVID-19 vaccine should not be withheld from pregnant women who meet criteria for vaccination.³

- The vaccine also should be offered to lactating women.⁴ There is potential for a vaccinated mother to make protective antibodies that are passed to her infant based on experience with other vaccines in pregnancy (such as influenza vaccines), although this has not been completely studied yet for the COVID-19 vaccine.

- The recommended considerations for vaccinating a pregnant woman against COVID-19 include the level of community transmission, her personal risks, and anticipated side effects, which are thought to be similar to other vaccines.

- If a fever develops, pregnant women may take acetaminophen.

- There is no need for a pregnancy test before vaccination.
FREQUENTLY ASKED QUESTIONS

Once vaccinated, do I need to wear a mask?
- Although the vaccines are highly protective, neither Pfizer nor Moderna vaccines provide 100% efficacy. We need more information to tell whether a vaccinated person can become infected without symptoms, or still pass the virus to others. This is being studied but it means we still have to wear masks after vaccination.

Can I get another vaccine at the same time as the COVID vaccine?
- The recommendation is to administer the COVID-19 vaccine alone, with minimal interval of 14 days from other vaccines. If accidentally done, neither vaccine should be re-administered.

What if I miss the window for the second dose?
- For either vaccine, if you miss the recommended timeframe for the second dose you should get it at the earliest opportunity. You do not need to restart the series.

Are the vaccines interchangeable?
- No, the two vaccines (Pfizer vs Moderna) are not interchangeable. If inadvertently done, no additional doses should be administered until more is known.

Are mRNA vaccines safe?
- Yes, these vaccines are safe, and they stimulate our body to make antibodies so our cells can fight off the SARS-CoV-2 virus that causes COVID-19 disease. The technology used to create them is not new, and is based on sequencing technology that has been around for years, but has not yet been used as part of a coordinated global effort to address a public health crisis such as this.
- Older vaccines like influenza require large amounts of live virus to be grown in special labs. This takes time and for COVID-19 would require extreme safety measures.
- The mRNA vaccines are not live virus, and are developed based on the sequence of the virus that is known. This makes vaccine development much faster, but still very accurate, and safe.

If I had COVID or was exposed to the virus, should I still get the vaccine?
- Yes, even those who had COVID-19 should be vaccinated once they are recovered. We do not yet know how long the immune response to natural infection lasts, and the vaccine has been shown to be effective in preventing infection.
- If you are acutely infected, you should wait until you have recovered to receive the vaccine.
- If you are recently exposed or in quarantine, you should wait until the end of quarantine to avoid exposure to healthcare workers.

If I had COVID or was exposed, do I need to get blood work done to look for antibodies before getting the vaccine?
- No, there is no need to evaluate for antibodies before vaccination.

If I have medical conditions, like diabetes or high blood pressure, should I get the vaccine?
- Yes! These medical conditions may result in a more severe infection with COVID-19 so it is important to get vaccinated.

If I am immunocompromised should I get the vaccine?
- There is limited data available, but vaccination may provide key protection against the virus in those with suppressed immune systems. The COVID-19 vaccines do not contain live virus.

Does either COVID-19 vaccine cause infertility?
- No, neither is linked to infertility. Despite social media chatter, antibodies to the spike protein have not been linked to infertility after COVID-19 infection, and there is no scientific reason to believe this will change after vaccination for COVID-19.
- No other viral infection or vaccination-inducing immunity by similar mechanisms has been shown to cause infertility.
- Women should feel comfortable that this claim has no basis in science.

Does the COVID-19 vaccine cause Bell’s palsy?
- This question comes from the side effects reported in the Moderna vaccine trial, which included 30,400 participants.
- Companies track every complaint, regardless of whether linked to vaccination.
- In the trial, 4 participants reported Bell’s palsy symptoms: 3 in the vaccine and 1 in the placebo group. This was not a significant difference, and thus was not attributed to the COVID-19 vaccine.

Will the vaccine cause male pattern hair growth?
- No, there is no evidence the vaccine causes women to grow beards or mustaches.
- In contrast, COVID-19 illness has been linked to hair loss.
- Thus, vaccination will not increase undesired hair growth and may prevent undesired hair loss from COVID-19.

How does the vaccination affect testing for COVID-19 disease?
- Vaccination will not affect results of nasal, nasopharyngeal, or saliva PCR or rapid antigen tests for diagnosis of acute infection.
- Currently, the antibody tests available in laboratories check for IgM or IgG to either spike or nucleocapsid proteins.
- Positive antibody (IgG) to spike protein could mean evidence of prior infection or vaccination.
- To document prior natural infection with live virus, laboratory evidence of antibody to nucleocapsid protein is needed.

How do I know if symptoms after vaccination are due to the vaccine or COVID-19 infection?
- Signs and symptoms unlikely to be from COVID-19 vaccination include: Cough, shortness of breath, rhinorrhea, sore throat, loss of taste or smell; Signs and symptoms that may be from either COVID-19 vaccination, SARS-CoV-2 infection, or another infection include: Fever, fatigue, headache, chills, myalgia, and/or arthralgia.

Who should not get the COVID vaccine?
- People who have had anaphylaxis or severe allergic reaction to any component of the vaccine.

References
Cervical cancer screening has substantially reduced cervical cancer incidence and mortality over the past few decades. From 1975 to 2017, the age-adjusted rate of new cases decreased from 14.8 to 6.3 per 100,000 persons, and the rate of mortality decreased from 5.5 to 2.2 per 100,000 persons. Cytology-based screening with the Papanicolaou (Pap) test has been used for several decades and is currently a part of screening programs worldwide. Clinicians also later discovered that carcinogenic variants of the human papillomavirus (HPV) cause a large proportion of cervical cancers, which led to the addition of HPV testing to screen for cervical cancer. Real-world data and health care providers continue to support cotesting as the most effective strategy for diagnosing cervical cancer and precancer in women.

In an interview with Contemporary OB/GYN®, Jessica Shepherd, MD, MBA, an obstetrician/gynecologist (OB/GYN) and minimally invasive surgeon at Baylor University Medical Center in Dallas, Texas, addressed topics related to cervical cancer screening. These included the benefits of cotesting with Pap and HPV tests over other screening strategies, support for cotesting among health care providers who specialize in women’s health, the effects of HPV vaccination on recommendations for cervical cancer screening, current disparities in incidence of and mortality from cervical cancer, and the role of OB/GYNs in protecting their patients’ health.

Guidelines for Cervical Cancer Screening

For screening in the general population, The American College of Obstetricians and Gynecologists (ACOG) and other leading societies recommend Pap testing alone every 3 years for women aged 21 to 29 years and cotesting with the Pap and HPV tests every 5 years for women aged 30 to 65 years. In 2018, US Preventive Services Task Force (USPSTF) updated their guidelines to state that screening with Pap testing every 3 years, cotesting with the Pap and HPV tests every 5 years, or HPV testing every 5 years were acceptable for average-risk women aged 30 to 65 years. In 2020, the American Cancer Society (ACS) updated their guidelines to propose shifting toward using HPV testing alone as the primary screening tool, delaying screening initiation for women until aged 25 years and having them undergo primary HPV testing every 5 years through aged 65 years; however, Shepherd stated that this recommendation is not...
in line with published data and real-world experience.°

“It seems illogical that eliminating screening options would lead to a decrease in cervical cancer,” she said. “Many health care providers as well as advocacy and women’s health organizations have spoken out against these proposed changes to reinforce their support for the proven Pap test. These voices are calling on ACOG to protect the role of the Pap test in cervical cancer screening guidelines.” Following the release of the recent ACS guidelines, ACOG issued a statement affirming support for their existing cervical cancer screening guidelines, which recommend use of the Pap test and cotesting to protect women.°

When consulting with patients in her practice, Shepherd said she usually recommends cotesting with the Pap and HPV tests because it can provide more information than HPV testing alone and doesn’t require additional samples from the patient. She added that Pap testing provides further benefits, including the detection of additional infections, gynecologic malignancies, and other asymptomatic cancers that may not be diagnosed otherwise.

Shepherd also pointed out that real-world data that are representative of screening in the United States support cotesting as the optimal strategy to assess disease risk and protect cervical health. Results from the largest and most diverse longitudinal cervical cancer screening study to date affirm that using a Pap test and HPV test together (ie, cotesting) is the most effective strategy for diagnosing cervical cancer and precancer in women. The Quest Diagnostics study showed that HPV testing alone missed twice as many women who developed cervical cancer compared to cotesting. Additionally, it demonstrated that the type of Pap test matters, with strong performance resulting from the use of image liquid-based cytology.°

Shepherd cautioned that using HPV testing alone could lead to missed diagnoses and more recommendations for colposcopies. A 2015 European multinational epidemiologic study showed that 90.4% of usual-type adenocarcinomas were HPV positive, and other less common adenocarcinoma subtypes had relatively low rates of HPV positivity (30.4% for serous, 27.6% for clear cell, and 12.9% for endometroid subtypes).° Shepherd emphasized that the rate of HPV-negative test results seen in the most common subtype of adenocarcinomas, although numerically small, is clinically meaningful. “A considerable number of invasive cancers, approximately 9% to 10%, test negative for HPV; meaning that HPV-alone testing could lead to a substantial amount of missed cases,” she said.

Shepherd added that countries that have shifted to testing with HPV alone have reported increases in follow-up procedures. A 2018 study estimating the impact of changes to Australia’s National Cervical Screening Program showed that the transition to HPV-alone testing has resulted in substantial overtreatment, with 1 colposcopy clinic in Australia reporting that the volume of referrals has increased 6 fold.° “Health care providers fear that HPV-alone testing would result in more missed diagnoses and more recommendations for colposcopies,” Shepherd said.

She added that the vast majority of OB/GYNs and other health care providers support cotesting for frontline cervical cancer screening. A 2020 survey from the National Association of Nurse Practitioners in Women’s Health and HealthyWomen of 751 health care providers that specialize in women’s health, family, or other specialties such as pediatrics, adult medicine, and gerontology, as identified by self-report (251 OB/GYNs, 250 nurse practitioners, and 250 primary care providers) showed that more than 90% of those surveyed stated that Pap testing was valuable and effective. Sixty-one percent stated that eliminating the Pap test from frontline screening for cervical cancer would have a negative effect on women’s health.° In addition, approximately 90% of all health care providers, including 91% of OB/GYNs, agreed that cotesting with HPV and Pap tests is valuable for managing patient health in women aged 30 to 65 years. Further, 81% of all OB/GYNs said that cotesting is the way they screen for cervical cancer in women aged 30 to 65 years. Fewer than 1 percent of health care providers said they screen using
HPV alone. The survey also included an online survey of a nationally representative sample of 1000 women aged 25 to 65 years; 90% of respondents agreed that Pap testing is important for the management of their overall health and well-being, and 68% agreed that eliminating the Pap test would negatively affect women’s health.

“These findings demonstrate the growing reliance on cotesting with the Pap test and HPV test together as the gold standard for preventing cervical cancer,” Shepherd said.

Although Shepherd said that HPV vaccination is important for disease prevention (of cervical cancer and HPV), she noted that rates of vaccination among adolescents are too low to move toward HPV-alone testing. In an analysis of data from the 2018 National Immunization Survey—Teen, published in Morbidity and Mortality Weekly Report, investigators estimated that 51.1% of adolescents aged 13 to 17 years were up-to-date with the HPV vaccine series, an increase from 48.6% in 2017 (increases were only observed among males). However, adherence is still not strong enough to support changing or limiting screening options, according to Shepherd.

“Additionally, a substantial number of women in their 40s and 50s never received any HPV vaccination when they were younger,” she said.

Shepherd added that there are “troubling disparities” in rates of cervical cancer among certain racial or ethnic groups. According to a CDC data analysis from 2008 to 2012 from population-based cancer registries that participate in the agency’s National Program of Cancer Registries (NPCR) and the National Cancer Institute’s SEER program, rates of HPV-associated cervical cancer were higher in Blacks than in Whites (9.2 vs 7.1 per 100,000 persons) and higher in Hispanics than in non-Hispanics (9.7 vs 7.1 per 100,000 persons). Further, data from United States Cancer Statistics showed that the 5-year relative survival rate was lower in Black women than in White women (58.4% vs 68.8%), based on estimates of cases reported by the NPCR from 2001 through the end of 2016. Low socioeconomic status has also been associated with an increased incidence of and mortality related to cervical cancer. A 2017 analysis of data from the national mortality database, the 1979-2011 National Longitudinal Mortality Study, and the SEER cancer registry database showed that the risk of cervical cancer was 2.7 times higher among women living in the most deprived neighborhoods compared with those living in the most affluent neighborhoods. Additionally, women in the most-deprived group had a 76% higher disease-related mortality rate than those in the most-advantaged group between 2009 and 2013. According to Shepherd, reducing barriers to screening is important to reduce this gap. The 2018 USPSTF guidelines state that loss to follow-up and disparities in treatment may also contribute to cervical cancer morbidity and mortality in underserved populations. The guidelines also emphasize the importance of implementing systems to ensure follow-up of abnormal results, appropriate treatment of pathology, and support for patients throughout their treatment.

“Improving insurance coverage and access to care is a crucial step to overcome cost concerns that cause some women to delay screening,” said Shepherd. “Rather than limiting screening options and putting these women at even greater risk, it is more important than ever to ensure we protect all proven screening options.”

Shepherd said that supporting the health of patients is a key role of OB/GYNs and added that women should prioritize wellness visits starting at aged 21 years. They should be able to talk with their OB/GYN openly about screening for cervical cancer as well as other women’s health issues, such as the prevention of breast cancer and screening for sexually transmitted infections.

“As OB/GYNs, the role that we play in protecting women’s health, in addition to cervical cancer screening, is providing a strong relationship between a woman and her OB/GYN, which is crucial to preventing cervical cancer and other diseases,” she explained. “Shared decision-making between OB/GYNs and women builds trust and represents the best way to protect cervical health.”

Shepherd added that OB/GYNs should play a major role in informing future updates to guidelines for cervical cancer screening because they are able to observe the importance of screening firsthand and are familiar with common concerns from patients.

“Any future evolution to screening guidelines and practices should account for the real-world experience of OB/GYNs and other women’s health providers to ensure proper compliance, screening effectiveness and, ultimately, the best protection for women’s health,” she said.

She concluded that with the challenges in providing preventive health care brought about by the coronavirus disease 2019 pandemic, protecting all screening options for cervical cancer is particularly important. “We call on ACOG to listen to OB/GYNs who are speaking out in favor of retaining the Pap test and cotesting in screening guidelines,” she said.
Shepherd discusses the benefits of cotesting with Papanicolaou and human papillomavirus (HPV) tests over other screening strategies, support for cotesting among health care providers specializing in women's health, effects of HPV vaccination on recommendations for cervical cancer screening, current disparities in incidence of and mortality from cervical cancer, and the role of OB/GYNs in protecting their patients’ health.

To see the full video with Shepherd, scan the code.

REFERENCES

Different and less diverse microbiota

by SANDRA FYFE

Vaginal microbiota in prepubescent girls with vulvovaginitis consists of different and less diverse flora than prepubescent girls without vulvovaginitis, according to a study published in the European Journal of Clinical Microbiology & Infectious Diseases.

Wu Xiaoming, MD, of the Department of Pediatric Gynecology at Beijing Children’s Hospital at Capital Medical University’s National Center for Children’s Health in China, and colleagues conducted the study. They noted that vulvovaginitis causes significant anxiety in children and their parents and that it is the most common gynecological disease in prepubescent girls.1 Vulvovaginitis causes inflammation of the vulva and vagina.

The authors said that behavioral issues, in addition to anatomic and physiological factors for girls this age, can cause changes in vaginal microbiota. “Disorders involving vaginal flora usually cause infectious clinical syndromes with irritating symptoms, such as vaginal discharge, external genital organ erythema, soreness, itch, irritation, dysuria, and bleeding,” the authors noted.1

Researchers collected samples from 10 girls with vulvovaginitis and 16 healthy girls aged 3 to 9 years. Researchers categorized the samples into 3 groups: healthy fecal swabs (HF), healthy vaginal swabs (HV), and vulvovaginitis swabs (VVS). Researchers used the NovaSeq 6000 SP500 platform to determine vaginal microbiota by sequencing the V3-V4 region of the 16S rRNA gene. The authors also analyzed intestinal microbiota of healthy girls to compare results.

Prevotella, Porphyromonas, Ezakiella, and Peptoniphilus were prevalent in healthy girls. Healthy girls also had more vaginal microbiota diversity. “The dominant taxa in the HF group were Bacteroides, Faecalibacterium, Blautia, and Bifidobacterium, which were not the main vaginal bacteria in children with vulvovaginitis,” the authors said.

Girls with vulvovaginitis had lower vaginal microbiota diversity, with Prevotella, Porphyromonas, Ezakiella, Peptoniphilus, Campylobacter, Anaerococcus, Dialister, Haemophilus, and Granulicatella prevalent. “Compared with the HVS group, some of the top 30 bacteria (Granulicatella, Streptococcus, Gardnerella, Haemophilus, Atopobium) were enriched (P < 0.05), while others (Prevotella, Porphyromonas, Ezakiella, Peptoniphilus, Campylobacter) were depleted in the VVS group (P < 0.05),” researchers reported.1

“Lactobacillus deficiency and high bacterial diversity were characteristics of the vaginal microbiome in healthy prepubertal girls; this is inconsistent with that in reproductive-age women,” the authors wrote, noting that the differences in microbiota were not fecal in origin.1 The study adds evidence that vulvovaginitis is caused by a disturbance in the vaginal microbiome. Because this microbiome has not been well defined in prepubescent girls, the purpose of this study was to document microbiota.

“Measures of alpha diversity indicated that the diversity of the vaginal microbiome in healthy prepubertal girls was high; vulvovaginitis-associated dysbiosis is generally characterized by loss of diversity and the presence of pathogens with high levels of abundance,” Xiaoming and colleagues concluded.

Sandra Fyfe is a freelance writer for Contemporary OB/GYN®.

FOR REFERENCES VISIT contemporaryobgyn.net/microbiota
Introduction
Inflammatory bowel disease (IBD) comprises ulcerative colitis and Crohn’s disease. In 2015, an estimated 1.3% of adults in the United States, or roughly 3 million people, were reported to have IBD.1 About half of those affected are female and the peak incidence of IBD is between 15 and 40 years old.2 Thus IBD in women tends to occur during their childbearing years when their most consistent health care provider is likely to be their obstetrician/gynecologist. In this article, we will review the basics of IBD and steps to optimize maternal and neonatal outcomes for women with IBD, including preconception counseling, medication management during pregnancy in conjunction with a gastroenterologist, and postpartum care.

IBD 101: The basics
Etiology and Risk Factors
While the exact etiology of IBD is unclear, it is widely thought to be a dysregulated host immune response to genetic, environmental, and microbial factors. Ten to 25% of affected patients have a family history of IBD.3 Certain environmental exposures such as frequent antibiotic use in childhood, low vitamin D levels, frequent nonsteroidal anti-inflammatory drug use, and diets high in processed, sugary, or fried foods may increase risk for IBD.3 Interestingly, smoking increases risk of Crohn’s disease while smoking cessation increases risk of ulcerative colitis.3 Breastfeeding may confer a protective benefit in development of IBD.4

Ulcerative Colitis
Patients with ulcerative colitis present with acute onset of bloody diarrhea, mucus, and urgency. Ulcerative colitis affects only the colon and a colonoscopy reveals inflammation in the form of ulcers starting in the rectum and extends in a contiguous manner more proximally (Picture 1). Ulcerative colitis is limited only to the mucosal layer of the colon wall. Despite having bloody diarrhea, patients rarely have anemia (Table 1).
For those with milder disease, the mainstay for therapy includes oral or rectal administration of 5-aminosalicylates. For those with more moderate to severe disease, immunomodulators (5-mercaptopurine or azathioprine) and biologic medications (Table 3) are more effective. Of note, steroids (prednisone, budesonide) are used only for flares and not for maintenance therapy.

Those with ulcerative colitis have an increased risk of colon cancer and require frequent colonoscopies, typically every 3 years, even if they are in remission, to evaluate for dysplasia. In medically refractory cases of ulcerative colitis or dysplasia, a multistage surgery that consists of complete removal of the colon and reconstruction of an ileal pouch anal anastomosis (IPAA) or “J-pouch” is recommended. Women who undergo all stages of this surgery do have a threefold decrease in fertility compared with age-matched women without this surgery because of extensive adhesions leading to tubal factor infertility.5

CROHN’S DISEASE
Crohn’s disease can occur anywhere in the gastrointestinal tract from mouth to anus, although the terminal ileum is the most common site. A typical presentation is slower onset of non-bloody diarrhea, abdominal pain, weight loss, malnutrition, anemia, and vitamin deficiencies. Classic colonoscopy findings include deeper ulcers with intervening areas of normal mucosa known as “skip lesions,” a cobblestone appearance, and a relatively normal appearing rectal area (Picture 2). While we are classically taught granulomas on biopsy are diagnostic of Crohn’s disease, less than one-third of biopsies show these findings (Table 1). Unlike in ulcerative colitis, oral 5-aminosalicylates are not found to be effective in Crohn’s disease, and biologics and/or immunomodulators are preferentially used.

Crohn’s affects all layers of the bowel wall, thus, complications like strictures, abscesses, and fistulas can occur. Of note, perianal disease occurs with Crohn’s disease and currently active perianal disease is an indication for cesarean delivery. Vulvar Crohn’s disease can occur with manifestation of linear “knife-like” vaginal fissures.

What is the difference between irritable bowel syndrome and inflammatory bowel disease?
IBD is often confused with irritable bowel syndrome (IBS) as there may be similar symptoms of abdominal pain and diarrhea but these are two very distinct entities with vastly different treatment and outcomes (Table 2). Irritable bowel syndrome is a functional disorder that is common in the general population with up to 10-15% affected in the United States. Risk factors include female sex, age under 50, concomitant anxiety or depression, and family history of IBS. IBS does not result in any endoscopic or imaging findings and has no increased risk of cancer. Mainstays of therapy for IBS include diet, exercise, fiber, and neuromodulating agents such as antidepressants.16

This is in contrast to IBD, which has visual endoscopic inflammation and can be seen on imaging studies. If IBD

<table>
<thead>
<tr>
<th>Table 1: ULCERATIVE COLITIS VS CROHN’S DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Bloody diarrhea, mucus, urgency</td>
</tr>
<tr>
<td>Malabsorption, weight loss</td>
</tr>
<tr>
<td>Extent of intestinal involvement</td>
</tr>
<tr>
<td>Depth of involvement</td>
</tr>
<tr>
<td>Rectal involvement</td>
</tr>
<tr>
<td>Endoscopic pattern</td>
</tr>
<tr>
<td>Granulomas</td>
</tr>
<tr>
<td>Abscess</td>
</tr>
<tr>
<td>Strictures</td>
</tr>
<tr>
<td>Fistulas</td>
</tr>
<tr>
<td>Vaginal involvement</td>
</tr>
<tr>
<td>Colon cancer risk</td>
</tr>
<tr>
<td>Perianal disease</td>
</tr>
</tbody>
</table>
is left untreated there is a risk for co-
lon cancer and complications such as 
strictures, abscess, and fistulas, as 
above. Medications for IBD include 
immunosuppressants.

Preconception counseling

ADVERSE PREGNANCY OUTCOMES WITH ACTIVE IBD

Women with active IBD at conception or those who flare during pregnancy are at increased risk for adverse outcomes including miscarriages, poor maternal weight gain, preterm birth, low birth weight infants, preeclampsia, and increased risk of cesarean delivery. 6-13 Data have shown that these risks are far lower in women who are in endoscopic remission prior to pregnancy and an updated colonoscopy should be performed in those contemplating pregnancy. For those women with IBD who are not yet optimized, we advocate counseling patients on safe and effective contraception. Intrauterine devices and implants are the preferred over combined hormonal contraceptives as women with IBD are higher risk for thromboembolic disease.14 Women with IBD are also higher risk for osteoporosis, thus, depot medroxyprogesterone acetate injections should be used with caution.15

TEAM APPROACH WITH OBSTETRICIAN, GASTROENTEROLOGIST, MATERNAL FETAL MEDICINE SPECIALIST

Because of these increased risks, preconception counseling is of utmost importance and, in fact, has been shown to improve outcomes by improving adherence with medications and decreasing flares during pregnancy.14 We advocate for a team approach with an obstetrician and/or maternal fetal medicine (MFM) along with a gastroenterologist for all patients with IBD as there are data that even those in remission can have some increased risk of flares and adverse outcomes.12 Discussion of safety of medications is often the focus for patients but providers should also counsel on the risks of flares and adverse outcomes of active inflammation if medications are decreased or discontinued. A consistent message to the patient is critical.

PRECONCEPTION TESTING

During preconception counseling, obtain baseline labs including inflammatory markers (sedimentation rate, C-reactive protein), a commonly utilized stool inflammatory marker (fecal calprotectin) and recent colonoscopy to ensure endoscopic remission.

IBD medications during pregnancy and breastfeeding

IBD MEDICATIONS TO AVOID

Nearly all IBD medications with few exceptions can be continued during pregnancy and breastfeeding (Table 3). The exceptions include methotrexate and thalidomide for their well-known teratogenic effects. Tofacitinib, a newer medication that was recently approved for ulcerative colitis, does not have enough data for comment on safety during pregnancy. These three medications should be avoided and patients who are on these and are contemplating pregnancy should be switched to a safer alternative that achieves endoscopic remission before conceiving.12

Table 2

<table>
<thead>
<tr>
<th>IBD vs. IBS</th>
<th>Inflammatory bowel disease (IBD)</th>
<th>Irritable bowel syndrome (IBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea, abdominal pain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Malabsorption, weight loss, anemia</td>
<td>Yes (Crohn’s disease)</td>
<td>No</td>
</tr>
<tr>
<td>Bloody stools</td>
<td>Yes (ulcerative colitis)</td>
<td>No</td>
</tr>
<tr>
<td>Visual inflammation seen on endoscopy/colonoscopy or on imaging</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment including anti-inflammatory medications such as steroids, immune suppressants</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Surgery is sometimes necessary</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevalence in United States</td>
<td>1%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Male/female predominance</td>
<td>Equal</td>
<td>More females</td>
</tr>
<tr>
<td>Triggered by stress</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fistulas, abscess, strictures, perianal disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Colon cancer risk</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
**IBD MEDICATIONS TO CONTINUE**

**5-AMINOSALICYLATES AND SULFASALAZINE.** These medications come in the form of oral tablets or rectal suppositories/enemas. They are commonly used for mild to moderate ulcerative colitis and less commonly for Crohn’s disease. They are low risk and can be continued during pregnancy. Pregnant women on sulfasalazine need increased folic acid supplementation of 2 mg daily. Reversible infant diarrhea has been reported in a few cases but these medications are considered compatible with breastfeeding.12

**IMMUNOMODULATORS: 6-MERCAPTOPURINE (6MP), AZATHIOPRINE.** These oral medications are used for moderate to severe ulcerative colitis and Crohn’s disease either as monotherapy or in combination with biologics. Recent data do not show any increased risk of congenital anomalies. Recommendations are to continue with these medications during pregnancy if used for monotherapy. In patients with combination therapy with biologics who are in deep remission, we can consider stopping these medications while continuing biologic monotherapy on a case-by-case basis in conjunction with the gastroenterologist. They are both compatible with breastfeeding.12

**BIOLOGIC MEDICATIONS.** These medications, which are either infusions or injections, are used for moderate to severe ulcerative colitis and Crohn’s disease. Three broad categories exist at this time: 1) tumor necrosis factor (TNF) inhibitors such as infliximab, adalimumab, certoli-

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<table>
<thead>
<tr>
<th>Table 3</th>
<th>IBD MEDICATION SAFETY DURING PREGNANCY AND BREASTFEEDING COMPATIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
<td><strong>Breastfeeding</strong></td>
</tr>
<tr>
<td>5-aminosalicylates</td>
<td></td>
</tr>
<tr>
<td>• Mesalamine</td>
<td>Low risk, continue</td>
</tr>
<tr>
<td>• Sulfasalazine</td>
<td>For sulfasalazine supplement with folate 2 mg/day</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Teratogenic</td>
</tr>
<tr>
<td></td>
<td>Abortifacient</td>
</tr>
<tr>
<td></td>
<td>Delay pregnancy for at least 3-6 months</td>
</tr>
<tr>
<td><strong>6-mercaptopurine, azathioprine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low risk in monotherapy, continue</td>
</tr>
<tr>
<td></td>
<td>Individualize dual therapy with biologics in certain patients in prolonged remission</td>
</tr>
<tr>
<td><strong>Anti-TNF biologics</strong></td>
<td></td>
</tr>
<tr>
<td>• Infliximab</td>
<td>Low risk in monotherapy, continue</td>
</tr>
<tr>
<td>• Adalimumab</td>
<td>Low or undetectable levels, compatible</td>
</tr>
<tr>
<td>• Golimumab</td>
<td></td>
</tr>
<tr>
<td>• Certolizumab (does not cross placenta)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-integrin biologics</strong></td>
<td></td>
</tr>
<tr>
<td>• Vedolizumab</td>
<td>Low risk in monotherapy, continue</td>
</tr>
<tr>
<td>• Natalizumab (rarely used)</td>
<td>Low or undetectable levels, compatible</td>
</tr>
<tr>
<td><strong>Anti-interleukin biologics</strong></td>
<td></td>
</tr>
<tr>
<td>• Ustekinumab</td>
<td>Low risk in monotherapy, continue</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Low or undetectable levels, compatible</td>
</tr>
</tbody>
</table>

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zumab, golimumab; 2) anti-integrins (vedolizumab, natalizumab); and 3) anti-interleukins (ustekinumab).

These are highly effective medications that should be continued in pregnancy. If doses are missed or an extended gap exists between doses, patients may develop antibodies to these medications that not only render them ineffective but also may actually cause a life-threatening allergic reaction on reexposure. Thus, it is imperative to be mindful of these medications and plan each dose during pregnancy and postpartum period.

Biologic medications used in IBD
are monoclonal antibodies and are actively transferred across the placenta, with the highest levels in the second and third trimester. While there are no known fetal adverse effects, it is ideal to time the final pregnancy dose more remote from the estimated delivery date to minimize the neonatal levels. The last dose of a biologic medication in pregnancy should be given roughly so that the next dose is a few days after delivery. For example, a standard infliximab dosing interval is every 8 weeks, therefore the last dose should be given around 32 weeks’ gestation and the subsequent dose 1-2 days postpartum assuming a 40-week delivery. While this is the ideal scenario for remission, if a patient is flaring during pregnancy, these medications are often increased and continued through the time of delivery.

Breastfeeding is compatible with all of the biologics as levels in the breast milk are exceedingly low or undetectable. Finally, infants exposed to these biologics should avoid live virus vaccines in the first 6 months of life. The exception to the above is certolizumab pegol, which is an injectable anti-TNF biologic approved for treatment of Crohn’s disease. Because it lacks a fragment crystallizable (Fc) region, it is the only biologic that does not cross the placenta, so fetal and neonatal exposure is negligible. Therefore dosing does not need to be timed with delivery and infant vaccine schedules are not altered. While the lack of transplacental transfer is a favorable characteristic of certolizumab, efficacy, cost, and other potential factors should be considered as well when choosing any biologic to find the best individualized options for patients.

STEROIDS. Prednisone or budesonide (a gastrointestinal tract–targeting oral steroid equivalent used for milder flares in IBD) are often used for flares in both ulcerative colitis and Crohn’s disease but should not be used for maintenance therapy. If patient is early in their pregnancy and requires steroids, escalation of maintenance biologic such as infliximab should be considered. Steroids during pregnancy come with well-known adverse effects but are effective in quickly controlling IBD flares. They are compatible with breastfeeding.

Monitoring IBD patients during pregnancy
For those IBD patients who are in endoscopic remission prior to pregnancy, are on stable medications, and do not flare, routine antepartum care is appropriate. We recommend a GI visit and a complete blood count with liver enzymes every trimester in conjunction with the routine OB labs and visits. The obstetrician can consider growth ultrasounds as necessary if pregnancy is progressing as planned. An examination of the perineum in those with Crohn’s disease is recommended to ensure no active disease is seen in the third trimester.

For those IBD patients who flare during pregnancy, close OB, GI, and MFM follow-ups are essential. The GI physician can obtain more specialized labs including stool tests for infections and stool inflammatory marker of calprotectin and adjust or start medications as needed to control the flare. From an OB and MFM standpoint, consider more frequent growth scans and if on steroids, closer glucose monitoring.

If there is a concern for a new diagnosis of IBD or a severe flare that requires initiation of biologics during pregnancy, an endoscopic procedure can be considered with strong preference for a shorter flexible sigmoidoscopy rather than a full colonoscopy. Flexible sigmoidoscopies can be done quickly without sedation or a preparation and be performed in the hospital GI lab setting rather than outpatient clinic office. However, routine GI procedures such as screening colonoscopies or nonurgent upper endoscopies should be deferred to the postpartum period. Any GI procedure during pregnancy should be done in coordination with the OB team.
Counseling patients with positive NIPT results can be complicated.

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Mosaicism Ratio adds an additional level of clarity. Rely on Labcorp/Integrated Genetics women’s health portfolio as your single-source for best-in-class screening, diagnostic testing, and all your needs across the entire pregnancy.

Reference:
**Young women better adhere to LARC over time**

*by BOB KRONEMYER*

Young women have significantly better adherence to long-acting reversible contraception (LARC) than to short-acting reversible contraception (SARC) at 12 months, according to a systemic review and meta-analysis.

However, the review in *The European Journal of Contraception & Reproductive Health Care* found that more women chose SARC despite pregnancy being rare with LARC.

The authors noted that a full 50% of all pregnancies worldwide are unintended, with an even higher rate in women aged 25 years and younger.

“We sought to identify which method of contraception was the most effective option to prevent unintended pregnancy in young women and adolescents,” wrote the authors, who searched, without language restrictions, the PubMed, Embase, Lilacs and Cochrane databases from inception to July 2020.

Nine of the 25 included studies compared LARC to SARC, whereas 16 of the studies evaluated LARC methods only. Most of the included studies were observational; only two were randomized controlled trials (RCTs): one comparing LARC to SARC and the other comparing different LARC methods.

The three LARC methods were the copper-bearing intrauterine device (Cu-IUD), the levonorgestrel-releasing intrauterine system (LNG-IUS), and subdermal contraceptive implants. SARC methods were defined as combined oral contraceptives, progestin-only oral contraceptives, depot medroxyprogesterone acetate, condoms, vaginal ring, and patch.

At 12 months, young women were much more likely to achieve adherence with LARC compared with SARC: relative risk (RR) 1.60; 95% confidence interval (CI): 1.21, 2.12; $I^2 = 88\%$.

This finding likely indicates a better unintended pregnancy prevention outcome for young women with LARC. Nonetheless, more young women chose SARC than LARC: RR 0.37; 95% CI: 0.17, 0.80; $I^2 = 99\%$.

The safety profile was similar among the three LARC methods, showing LARC to be safe with few adverse events. The subdermal implant had the greatest uptake among the LARC methods, while the LNG-IUS was the most popular intrauterine contraceptive device (IUD).

Among LARC methods, the LNG-IUS was more efficacious than the Cu-IUD. Conversely, subdermal implants were more efficacious than IUCDs.

“However, all these differences are small and not clinically relevant,” the authors wrote.

To decrease the risk of sexually transmitted infections, health care providers should remind sexually active adolescents to consistently use male latex condoms in conjunction with LARC or any other nonbarrier methods, the authors noted.

Due to the low adoption of LARC methods by young women, several of the studies underscored the importance of continual training and updating of health care providers, because their knowledge, attitudes, and comfort with LARC methods can impact LARC uptake.

Implementing education programs directed at adolescent girls about the benefits of LARC is crucial.

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

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In this Contemporary OB/GYN® K-Cast expert video series, Vincenzo Berghella, MD, and Amanda Roman-Camargo, MD, discuss complications, risk factors, management, prevention initiatives, treatment guidelines, and available tests for diagnosis.

Watch now:
contemporaryobgyn.net/prom-advances
Perimenopausal abnormal uterine bleeding

The challenge of diagnosis occurs in distinguishing “normal” from “abnormal” in a time of rapid and dynamic change.

by NANETTE SANTORO, MD, AND ELIZABETH CLAIN, MD

Introduction

CASE VIGNETTES

1. A 48-year-old woman reports that her menstrual cycles have gone from a mean of 30 days to 25 days, and her menstrual periods have lengthened to 10 days from 5 days, with intermittent very heavy bleeding (more than 2 pads or tampons per hour for more than 4 hours) and staining of her bedsheets with blood. She does not report cramping in association with bleeding. On examination, her uterus is irregular and 10 weeks’ size. A pelvic ultrasound indicates 2 fibroids, both 4-5 cm in mean diameter. One is clearly intramural and the second fibroid appears to be encroaching on the endometrial stripe, which is irregular and 8mm in largest thickness. Ovaries appear normal sized with an antral follicle count of 7.

2. A 52-year-old woman who had an endometrial ablation at age 45 for menorrhagia presents with irregular spotting for the past 3 months. She reports some cramping in association with her spotting, along with a dull ache in her left lower quadrant. Her pelvic examination is negative and an ultrasound indicates an irregular endometrium with ‘skip areas’. The thickest portion of the endometrium that can be identified in sagittal section is 3mm. The remainder of her ultrasound examination is within normal limits.

Prevalence and causes of abnormal uterine bleeding

Perimenopausal bleeding is challenging to define because distinguishing normal from abnormal uterine bleeding (AUB) during a time in life when a woman’s menstrual cycles are dynamically changing requires an extra degree of clinical acumen and attention. The American College of Obstetricians and Gynecologists (ACOG) defines AUB as: ‘bleeding from the uterine corpus that is abnormal in its regularity, volume, frequency or duration and is not associated with pregnancy.’

by NANETTE SANTORO, MD, AND ELIZABETH CLAIN, MD

NANETTE SANTORO, MD is professor and E. Stewart Taylor Chair of Obstetrics & Gynecology at the University of Colorado School of Medicine in Aurora, Colo.

ELIZABETH CLAIN, MD is a fourth-year resident in the Department of Obstetrics and Gynecology at the University of Colorado School of Medicine in Aurora, Colo.
This entity is further separated into acute AUB, which requires immediate assessment of the patient’s hemodynamic stability and consideration of acute management modalities, and chronic AUB, which is defined as AUB that is present for most of the past 6 months. Regardless of acute or chronic nature, the differential diagnosis is the same and the PALM-COEIN diagnostic has been adopted by ACOG as a preferred classification system (Figure 1).² The ‘PALM’ refers to uterine structural abnormalities and the ‘COEIN’ refers to conditions unrelated to structural abnormalities of the uterus. It is assumed that pregnancy has been excluded once PALM-COEIN has been invoked as a diagnostic tool.

The prevalence of AUB is 3-30%, with higher prevalences clustering at the extremes of reproductive life—perimenarche and perimenopause.² Perimenopausal women may experience menstrual irregularities consisting of shortened menstrual cycles and cycles with or without ovulation.² Both short (<21 days) and long (>36 days) cycles are associated with anovulatory patterns of progesterone secretion. Anovulatory cycles are more likely to be associated with spotting. Some shortened menstrual cycles are the result of the so-called LOOP—luteal-out-of-phase phenomenon, in which folliculogenesis begins during the luteal phase preceding menses.¹ Anovulatory cycles have been associated with heavier bleeding that is typically sporadic but may be acute. Thus, some AUB in the perimenopausalmay be physiologic. Structural lesions of the uterus (PALM) such as polyps, adenomyosis, leiomyomata, and malignancy are not uncommon in women in the perimenopausal years.

**POLYPS.** In a cohort of 64 asymptomatic women with a mean age of 44, 16% were observed to have polyps.⁵ Another sample of 112 reproductive-aged women with endometrial polyps followed over almost 2 years indicated that 15% developed AUB.⁶

**ADENOMYOSIS.** Adenomyosis has a prevalence ranging from 5-70%; however, 70-80% of women who undergo hysterectomy for adenomyosis are in the 4th-5th decade of life.⁷ Thus, adenomyosis appears to cause the most symptoms around perimenopause. Some argue that adenomyosis, present in 48% of hysterectomy specimens, is not necessarily associated with bleeding and may be a normal variant and not a disease.⁸ However, AUB attributed to adenomyosis is usually not amenable to medical management and often requires surgical treatment.

**LEIOMYOMATA.** In a population-based sample of 650,000 U.S. women age 18-65 in the Kaiser Permanente Washington system, 15.9% of women aged 50-54 had leiomyomata, the highest prevalence in the sample; peak incidence rates were at ages 45-49.⁹ These numbers align with the sample of de Waay, et al, in which 23% of women had leiomyomata by ultrasound.³ The growth rate of leiomyomata was faster in premenopausal women and slower in women who were closer to their final menstrual period.

**MALIGNANCY.** The average age at diagnosis for endometrial cancer is 60, and cases are relatively uncommon prior to age 45.¹⁰ Clinically, it is recommended that perimenopausal women with AUB be screened with endometrial sampling to rule out cancer (see below). Since bleeding patterns are inherently irregular for perimenopausal women, and dysfunctional uterine bleeding due to anovulation can cause isolated episodes of heavy bleeding, many women undergo endometrial sampling but very few will actually have hyperplasia or cancer.

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**Figure 1. The PALM-COEIN system is used to classify causes of abnormal bleeding in nonpregnant premenopausal women.**

Risk factors for endometrial cancer are provided in Table 1.

**THE OTHER SIDE OF THE COEIN.** Coagulopathies are usually diagnosed earlier in life; however, perimenopausal women can acquire them. Von Willebrand’s Disease (vWD) is present in 1% of women, and 95% of women with vWD report heavy menstrual bleeding. Platelet dysfunction can be present in vWD and immune thrombocytopenia, which has an overall prevalence of 1/10,000, increases in prevalence with age. Ovulatory disorders, described above, are relatively common in perimenopausal women. Up to 7% of women have polycystic ovary syndrome (PCOS) and are chronically anovulatory. Endometrial causes include chronic endometritis. The true prevalence of chronic endometritis and its histologic definition are not well established, but the diagnosis should be suspected in women with intermenstrual bleeding and overall mild symptoms. Other forms of endometrial dysfunction and failure of the normal hemostatic mechanisms that allow menses to stop are poorly understood but seem to be responsible for some cases of AUB in the perimenopause. Therapeutic anticoagulation and chemotherapy-associated thrombocytopenia are potential iatrogenic causes of AUB, as are any type of exogenous hormone therapy that can cause breakthrough bleeding. Some medications also can interfere with normal menstrual cycling, such as dopamine antagonists, and result in acyclic, anovulatory bleeding (but more often cause oligomenorrhea). Finally, a category of ‘Not Otherwise Classified’ disorders are responsible for the remainder of cases. These latter conditions are rare but can include bleeding from Cesarean scar related uterine diverticula, which accumulate blood and sporadically cause spotting.

**Clinical Management**
**EVALUATION AND WORKUP**
Discussion of patient history should include review of the patient’s bleeding pattern, contraceptive use, risk factors for endometrial cancer, medical problems, personal or family history of underlying bleeding disorders, and current medications. Physical exam should include speculum and bimanual exams and thyroid exam. Laboratory testing may include a complete blood count, pregnancy testing, coagulation studies, assessment for bleeding disorders such as vWD, and thyroid screening. Patients with acute bleeding who are hemodynamically unstable require surgical management or high-dose estrogen treatment and will not be discussed further in this review.

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With just one sample, the Aptima® Multitest Swab simplifies testing and provides more answers for sexual and vaginal health. The vaginal swab is the preferred collection method of the CDC and patients for chlamydia and gonorrhea. It can also be used to detect up to 7 infections and disease states.

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References:
assessed with ultrasound, which may also guide the need for endometrial sampling to evaluate for hyperplasia or malignancy. If possible, ultrasound performed 4-6 days after onset of bleeding will yield maximum information about the endometrium. If the endometrial stripe is irregular or not clearly identified, sonohysterography can help distinguish between global and focal changes. Generally, endometrial sampling should be performed in women over 45 years old with AUB, and those younger than 45 with a history of unopposed estrogen exposure, risk factors for endometrial cancer, or failed medical management. Significant focal pathology, such as polyps or submucosal myomas, will likely be missed by a blind endometrial biopsy. Hysteroscopy may be indicated in selected cases when focal disease is strongly suspected or visualized on ultrasound; however, it is more expensive and invasive.15,16

Evaluation of the likely time until menopause can be helpful when discussing treatment options. Women who are close to menopause may prefer temporizing medical management to avoid surgery, while those for whom menopause is more distant may prioritize efficacy over limiting invasive procedures. An anti-Mullerian hormone (AMH) level >200 ng/mL makes menopause highly unlikely within the next five years, regardless of a woman’s age, whereas a very low AMH level predicts menopause in next year with a positive predictive value ranging from 51% at <48 years of age to 79% at ≥51 years of age.17,18

**Treatment**

**SURVEILLANCE**

If hyperplasia and malignancy have been ruled out, and the patient is not anemic, reassurance and surveillance are sufficient if the bleeding pattern is not too bothersome.13

**MEDICAL MANAGEMENT**

Hormonal treatments are the mainstay of medical management for AUB, and many simultaneously provide reliable contraception.

Combined hormonal contracep-
tives (including pills, vaginal ring, and patches) are effective for managing many etiologies of AUB and will alleviate vasomotor symptoms and vaginal dryness associated with perimenopause, particularly with extended or continuous dosing. Furthermore, they reduce the risk of endometrial and ovarian cancers and can maintain or improve bone mineral density. However, estrogen-containing hormonal contraceptives increase risk of thrombotic stroke and myocardial infarction, both of which increase in terms of background risk with age. Older reproductive-aged women are also more likely to have medical comorbidities including hypertension, obesity, diabetes, and cardiac disease that may contraindicate the use of contraceptive doses of estrogen.

Progestin-only methods have fewer contraindications and risks than estrogen-containing methods while still providing excellent contraception. These include progestin-only pills, injectables (depot medroxyprogesterone acetate), etonogestrel-containing implants, and the levonorgestrel intrauterine system (LNG-IUS). The LNG-IUS and POPs can also be continued into menopause to provide endometrial protection for women using estrogen to treat menopausal symptoms. Drawbacks include lack of efficacy for hypoestrogenic menopausal symptoms and an increased risk of irregular bleeding patterns.

The timing of discontinuing hormonal contraception in perimenopausal women is not straightforward. Women using LNG-IUS or etonogestrel-containing implants may experience amenorrhea prior to menopause, and women using combined hormonal contraception can experience withdrawal bleeding even after menopause. Discontinuing hormonal treatment to assess for 12 months of amenorrhea, which defines a woman as menopausal, leaves that woman at risk of unwanted pregnancy. For women using combined hormonal contraceptives, an age-based shared decision on when to stop can be used, taking into account the woman’s family history.

Use of AMH or FSH (³ 30 IU/l on two occasions 6-8 weeks apart, measured 7-14 days after discontinuation of hormones) have been described, but these biochemical methods have not been validated in large, diverse populations of women and therefore cannot be considered definitive. Women using LNG-IUS can start hormone replacement therapy (HRT) as needed while continuing use of the IUS.

Gonadotropin-releasing hormone (GnRH) analogues can induce a hypoestrogenal state that leads to endometrial atrophy. Agonists are available in injectable form (leuprolide acetate) and newer, orally active antagonists (elagolix) have recently been FDA approved for use in women with endometriosis. Long-term use of these compounds is limited by hypoestrogenic side effects including bone loss, vasomotor symptoms, and vaginal atrophy, but they can be useful in bridging women to menopause. "Add-back" therapy with low-dose norethindrone and estrogen can minimize side effects and bone demineralization. Elagolix is now available in a combined capsule with estradiol 1mg and norethindrone acetate 0.5mg. It is FDA approved for women with uterine fibroids who have excessively heavy bleeding.

For women with contraindications or objections to hormonal therapy, scheduled NSAIDs or tranexamic acid can significantly reduce menstrual blood loss.

RISK FACTORS FOR ENDOMETRIAL CANCER

- Chronic anovulation (PCOS)
- Early age at menarche and late age at menopause
- Older age
- High fat diet
- Low levels of physical activity
- Nulliparity
- Estrogen secreting tumors of the ovary (granulosa tumors)
- Insulin resistance and type 2 diabetes
- Personal prior history of epithelial cancers of breast or ovary
- Family history of endometrial or epithelial cancers of the colon, breast, or ovary
- Unopposed estrogen or certain SERM use (i.e., tamoxifen)
- History of endometrial hyperplasia
- Prior pelvic radiation

SOURCE: www.cancer.org/cancer/endometrial-cancer/about/key-statistics

HYSTEROSCOPY

Uterine polyps and submucosal fibroids can usually be effectively and efficiently treated with hysteroscopic removal. Incomplete removal and regrowth can cause recurrent bleeding. Polyps have been reported to have a cumulative incidence rate as high as 12% per year; thus, recurrent AUB in a woman previously treated for polyps should be managed proactively.

ABLATION

Endometrial ablation or resection provides a significant reduction in bleeding for many women, with a shorter recovery time and quicker return to work than hysterectomy, and comparable patient satisfaction rates. However, approximately 20% of women...
who undergo endometrial ablation will later have a hysterectomy. Ab-
lation makes later evaluation of the endometrium challenging and some-
times impossible, leaving women at risk of postmenopausal bleeding that
cannot be adequately evaluated as well as endometrial cancers that pres-
ent late due to lack of bleeding.

**UTERINE ARTERY EMBOLIZATION (UAE) AND FOCUSED ULTRASOUND**

UAE is an interventional radiology procedure by which the uterine ar-
teries are occluded, with the aim of causing fibroid necrosis. UAE is as-
sociated with a shorter hospital stay and quicker return to full activity, but
an increased risk of minor complic-
ations compared to hysterectomy, and had comparable satisfaction and quality of life scores in a randomized study. Among those who underwent UAE, 24% had a hysterectomy by the 5th postoperative year and 35% by the 10th. A recent, randomized, con-
trolled trial of UAE versus MR-focused ultrasound reported similar out-
comes, although UAE had a lower rate of reintervention.

**HYSTERECTOMY**

While hysterectomy is the definitive treatment for abnormal bleeding, it carries an approximately 8% risk of complications, so it is best reserved for patients who have failed conservative management.

**Case-Based Management Considerations**

**CASE 1**

This patient’s changing bleeding pattern may be partially attributed to her peri-
menopausal status, but there is likely a contribution from her fibroids. Proges-
terone-only pills such as norethindrone may decrease her bleeding, although fibroids may grow and she is at risk of both hypoestrogenism with menopausal symptoms and an irregular bleeding pattern. DMPS or etonogestrel implant would offer contraception but could have more pronounced hypoestrogenic side effects and irregular bleeding than pills. Combined estrogen-progesterone methods may have a better bleeding profile, providing she has no contrain-
dications. If her uterine cavity is not signif-
ificantly distorted, an LNG-IUD can offer bleeding control and contraception with less risk of hypoestrogenism. The new combination of elagolix and low dose estradiol with norethindrone may provide bleeding control and bridge the patient to menopause. Prior to consider-
ing a hysterectomy, UAE is another po-
tential non-surgical option.

**CASE 2**

A crucial first step for this patient is as-
ssessing her menopausal status. If she is not yet menopausal, it is reasonable to observe her. However, if she is post-
menopausal or menopausal status is unclear, an endometrial evaluation is needed. There is no “normal” endo-
metrial thickness for a post-ablation uterus, therefore ultrasound alone is not sufficient. Endometrial biopsy via Pipelle catheter can be attempted, but is often unsuccessful, and may not evaluate the whole uterus. Hyst-
eroscopy with directed biopsies is the best choice for sampling but may be difficult due to obstructive scarring. If the entire cavity cannot be visualized, a hysterectomy must be considered.

**TAKEAWAYS**

1. Perimenopausal bleeding can be due to structural causes (polyps, adenomyosis, leiomyomas, malignancy) or non-structural causes (coagulopathy, ovulatory dysfunction, endometrial factors, iatrogenic, or “not otherwise classified”). Malignancy and ovulatory dysfunction in particular are more common in this population.
2. Initial evaluation includes history & physical, ultrasound, and possible saline infusion sonohysterography or endometrial biopsy.
3. Hormonal treatments can be used, just as with premenopausal women, but more frequent comorbidities and a possible need to transition to hormone replacement therapy may influence the choice of treatment. Newer oral GnRH analogues may be useful as well.
4. Procedures such as hysteroscopic polypectomy, endometrial ablation, and uterine artery embolization can be considered when hormones are not helpful or contraindicated, though ablation in particular can make later evaluation of the endometrium challenging.
5. Hysterectomy remains a reasonable choice for women who have failed more conservative management.
Uterine fibroids are hormone-driven diseases that can be estimated to affect approximately 70% to 80% of women by the onset of menopause. Although they often cause no symptoms, uterine fibroids, depending on their location and number, may cause some women to experience heavy bleeding, pelvic pain, and lower back pain, which can have a notable impact on quality of life. Fibroid size, often exceeding 10 cm in diameter, can lead to other direct symptoms, including abdominal protrusion, pelvic pressure, urinary urgency and frequency, incontinence, constipation, and/or tenesmus. Additionally, uterine fibroids are seen in approximately 10% of infertility cases and are associated with several pregnancy-related complications, such as spontaneous abortion, preterm delivery, and cesarean delivery.

According to Ayman Al-Hendy, MD, a professor of obstetrics and gynecology at The University of Chicago Pritzker School of Medicine, and Magdy Milad, MD, chief of Gynecology and Gynecologic Surgery at Northwestern Memorial Hospital in Chicago, the goals of treating uterine fibroids is to relieve the symptoms in a way in which the benefits outweigh the risks and side effects while maintaining quality of life. In a new video available at www.contemporaryobgyn.net/k-cast/management-of-uterine-fibroids, Drs. Al-Hendy and Milad discuss the current challenges and standards of care, as well as future opportunities in the management of patients with uterine fibroids. This article recaps key points from the conversation.

Risk Factors and Treatment Options

Several risk factors for uterine fibroids are worth noting. Increased age, hypertension, breast cancer, and ovarian cancer are each associated with a higher likelihood of uterine fibroids. Notably, there is a relationship between race and prevalence of uterine fibroids. In general, women of color tend to have a higher risk of uterine fibroids compared to their White counterparts,” Dr. Al-Hendy notes. “The risk factor in African American women or Black women is about 4 times more than European American or Caucasian women. In Hispanic women, it’s probably around 2.5 times.”

A negative correlation between serum vitamin D levels and total uterine fibroid volume has also been noted. “Vitamin D deficiency is now a well-recognized risk factor for uterine fibroids, and it’s very likely contributing to that first factor that I mentioned because as you know, we get our vitamin D from the sun mostly, and when you have darker skin, you don’t utilize the ultraviolet rays from the sun as effectively.”

Other risk factors include obesity and family history of uterine fibroids. “More recently, some research suggests that adolescent menorrhagia, or young women or adolescent girls who have heavy menstrual bleeding even before they have fibroids, is [a risk factor for] developing fibroids later on in life,” says Dr. Al-Hendy.

The goal of therapy is to relieve the signs and symptoms associated with the patient’s complaint, whether it’s menstrual bleeding, pelvic pain, bulk...
Current Management of Uterine Fibroids

symptoms, or infertility. According to Dr. Milad, the risk–benefit ratio is a key consideration no matter what therapy is instituted. “Ideally, therapy would sustain reduction in the size of the fibroids, prohibit fibroid growth, and maintain quality of life, including, for example, bone health.” To achieve optimal treatment, Dr. Milad states that shared decision-making is critical. “Shared decision-making is a process [in which] clinicians empower their patients to make optimal health care decisions that align with their priorities, so the burden is really on the clinician.” According to Dr. Milad, clinicians should help the patient clarify her goals, offer reasonable options, and explain the risks associated with those options, framing it in such a way that the patient can make her own decision. “This type of individualized care leads to high satisfaction and virtually eliminates the concerns regarding regret,” says Dr. Milad.

Regarding the treatment of bleeding, Dr. Al-Hendy points out that hormones can help make the endometrium thinner and potentially decrease the amount of bleeding, despite not really treating the fibroids themselves. Thus, oral contraceptives have been used to reduce blood loss from fibroids.2 “We’ve been using medications such as oral contraceptives for that purpose because the progesterone component works on the endometrium, makes it thinner, and tends to help with the bleeding, at least temporarily,” says Dr. Al-Hendy. Another approach to managing bleeding is with intrauterine devices (IUDs), which also reduce blood loss and decrease fibroid volume.2 Although clinical trials indicate that oral contraceptives and IUDs show efficacy initially, Dr. Al-Hendy notes that response tends to fail; the heavy bleeding returns, along with the potential adverse effects, rendering an IUD’s utility short term. Other potential therapies for uterine fibroids include selective progesterone receptor modulators (SPRM), which reduce blood loss and serve as an effective preoperative treatment; SPRMs are also not associated with hypoestrogenic side effects.2 However, none of these compounds are currently approved in the US. Another agent that’s been evaluated for the reduction of heavy bleeding is tranexamic acid. “[This agent] works mainly on the clotting fibrinolytic system and tries to inhibit fibrinolysis, and as such, it decreases the amount of bleeding,” says Dr. Al-Hendy. “The early clinical studies suggest some efficacy. Although in fibroid patients, it has been very limited.”

Surgical Options for the Treatment of Uterine Fibroids

Beyond traditional pharmacological and device-based treatments, surgical interventions are commonly performed for uterine fibroids. Uterine fibroids are the most common cause for hysterectomy in the United States, accounting for approximately 30% to 50% of all procedures.1 Another surgical option is myomectomy, a surgical or endoscopic excision of tumors that preserves fertility. It is worth mentioning, however, that repeated myomectomies can significantly increase risk of complications, such as pelvic adhesions.1 Careful planning and understanding of the location, number, and size of the uterine fibroids, along with other factors, are essential in the decision to treat uterine fibroids surgically, according to Dr. Milad. “While ultrasound can be helpful, MRI is really the gold standard, particularly when considering myomectomy,” he says. “It allows optimizing the surgical approach, whether it’s hysteroscopy, laparoscopy with or without robotic assistance, minilaparotomy, [or] traditional laparotomy, and it may also prompt preoperative suppression to reduce bulk.”

It is also important to note that not all patients are candidates for surgical procedures, and the potential for adverse events must be considered. “The ideal surgical patient is free of all comorbidities; has no evidence of diabetes, high blood pressure, and thromboembolic disease; is not anemic; and has no previous surgery or history of pelvic adhesive disease,” notes Dr. Milad. “Some people estimate that the complication rate for myomectomy and hysterectomy may be as high as 5%.”

Long-term complications remain an area of continued inquiry and discovery and should also be a concern when considering hysterectomies,

“Shared decision-making is a process [in which] clinicians empower their patients to make optimal health care decisions that align with their priorities, so the burden is really on the clinician... This type of individualized care leads to high satisfaction and virtually eliminates the concerns regarding regret.”
according to Dr. Al-Hendy. “It seems like we don’t [fully understand] the effect of that because some of those epidemiological data suggest increased risk for dementia and some [risk for] depression and [decrease in] cognitive function in women who had hysterectomy versus those who didn’t, even when you rule out contribution of the oophorectomy part,” says Dr. Al-Hendy. “I want to highlight some of the recent work, mostly coming from Mayo Clinic but also now being confirmed by other centers; when they looked at the long-term records of patients who had hysterectomy 20, 30 years earlier, and they’re looking at the incidence of heart disease, cognitive disorders, such as dementia, etc; the risk of dementia and heart disease is actually higher in those who had hysterectomy, even after you exclude the oophorectomy contribution. It suggests that maybe we don’t really have full understanding at the biological and molecular level of the contribution of the uterus. Maybe it does more than just harbor the baby during pregnancy, etc.”

**The Evolving Role of GnRH Antagonists**

In recent years, gonadotropin-releasing hormone (GnRH) antagonists have emerged as a unique class of oral drugs for the treatment of uterine fibroids. “[GnRH receptor antagonists] are nonpeptide compounds, and because they are nonpeptide, we can actually take them orally without [them] being digested or destroyed by the [gastrointestinal] enzymes,” notes Dr. Al-Hendy. “That’s a major advancement in the field, much more convenient for the patient, and hopefully will help the compliance.”

The other main distinction of GnRH antagonists is that they bind to the receptor immediately, and within a few hours, inhibit the release of the GnRH-releasing hormone. “Eventually, it leads to a decrease in [follicle-stimulating hormone] and [luteinizing hormone], suppresses folliculogenesis and ovulation, and then suppresses estrogen and progesterone production. This family of compounds works directly and without having this flare issue,” Dr. Al-Hendy explains.

GnRH antagonists should not be used long term as monotherapies, according to Dr. Al-Hendy. To achieve that window of therapeutic efficacy without suffering the adverse effects, he says you need approximately 40 to 60 pg/mL of estrogen. “These compounds are used to bring the estrogen level down, but then we add to all of them a very little amount of estradiol, typically 1 mg, and 0.5 mg of norethindrone acetate, progestin, all together to achieve the target, which is bringing the estrogen to the therapeutic range while not suffering or causing the undesirable side effects,” Dr. Al-Hendy explains.

Elagolix is the first and only GnRH antagonist to have achieved FDA approval for the treatment of heavy menstrual bleeding associated with uterine fibroids. However, agents within this class, relugolix and linzagolix, are completing clinical trials and undergoing evaluation for potential FDA approval. “This family of compounds has been developed through rigorous phase 3 placebo-controlled clinical trials in a large number of fibroid patients,” notes Dr. Al-Hendy.

In the pivotal Elaris Uterine Fibroids 1 and 2 (UF-1 and UF-2) trials, researchers randomized patients to receive elagolix 300 mg twice daily with once-daily hormonal add-back therapy or placebo. Among the women who received elagolix, the primary end point was met in 84.1% of women in UF-1 and in 77% of women in UF-2. “The vast majority of patients in those studies managed to normalize their heaviness of bleeding back to the normal range. Some patients in those studies who had very heavy bleeding, up to 90% of them up to 1 year of treatment, their menstrual blood loss was back to the normal range,” says Dr. Al-Hendy. Additionally, while amenorrhea might not be the main goal for many patients, approximately 50% of the patients achieved amenorrhea. Furthermore, fifty percent of the patients who started with anemia managed to cure or correct their hemoglobin levels. Dr. Al-Hendy adds that the adverse event profile for elagolix is tolerable. “There was an increase in the hot flash range, roughly around 20% versus around 11% in the placebo group, but most of these incidents were mild and a single incident per day.”

See the Complete Program at ContemporaryOBGYN.net.

To watch the full discussion between Dr. Al-Hendy and Dr. Milad, visit www.contemporaryobgyn.net/k-cast/management-of-uterine-fibroids
The efficacy and safety of investigational agent relugolix combination therapy (relugolix 40 mg plus estradiol 1 mg and norethindrone acetate 0.5 mg) has been studied in two Phase 3 trials, LIBERTY 1 and LIBERTY 2. Findings from the LIBERTY 1 and 2 studies demonstrated that relugolix combination therapy met the responder criteria \( (P < 0.0001) \), with 73.4% and 71.2% of women achieving the primary end point of reducing their menstrual blood loss to <80mL and by at least 50% from baseline compared with 18.9% and 14.7% of women receiving placebo, respectively.\(^4\) On average, women receiving relugolix combination therapy in both studies experienced an 84.3% reduction in menstrual blood loss from baseline \( (P < 0.0001) \). Dr. Al-Hendy notes that hemoglobin levels improved in women with anemia at baseline, and the amenorrhea rate was roughly around 50% in this program.

The LIBERTY trials are also notable because they evaluated pain, according to Dr. Al-Hendy. “From those patients who started with moderate or severe pain, based on a numerical rating scale that’s called NRS, about 50% of [them] managed to bring their pain to 0 or 1, which is considered minimal or non-existing pain.” The overall incidence of adverse events between relugolix combination therapy and placebo was comparable. The most common adverse reaction was hot flush. Additionally, bone mineral density was preserved after 1 year of treatment.

Phase 3 data for the investigational agent linzagolix with and without hormonal add-back therapy were presented at the 2020 ASRM Scientific Congress. Linzagolix was associated with a significantly improved menstrual bleeding and other symptoms of uterine fibroids at 24 weeks, with results being maintained at 52 weeks.\(^4\) In PRIMROSE 1, results showed responder rates of 56%, 67%, 71%, and 76% in the 100 mg, 100 mg plus hormonal add-back therapy, 200 mg, and 200 mg plus hormonal add-back therapy groups, respectively.\(^5\) In the PRIMROSE 2 trial, results showed responder rates of 57%, 77%, 78%, and 94% in the 100 mg, 100 mg plus hormonal add-back therapy, 200 mg, and 200 mg plus hormonal add-back therapy groups, respectively.\(^5\)

### Future Directions and Considerations

Women wait an average of 3.6 years before seeking treatment for uterine fibroids–related symptoms, and 41% of those seek treatment from at least 2 health care providers before diagnosis.\(^5\) Many who do seek treatment pursue surgical approaches. “We think that 1 in 3 women may undergo a hysterectomy by the age of 60, [which] highlights the need to follow [the American College of Obstetricians and Gynecologists] guidelines and offer alternative therapies before hysterectomy,” says Dr. Milad. Thus, it is important to increase awareness among patients regarding the growing treatment spectrum for uterine fibroids. Newer modalities, such as GnRH antagonists, present clinicians and patients with alternatives to surgical treatment.

The need for nonsurgical interventions will likely continue to expand. “It’s not uncommon to see women who are interested in retaining their uterus but not for fertility. We recently performed a study that suggested that in a subset of women, body image and sexual function play a role in choosing between conservative therapies and hysterectomy,” Dr. Milad explains.

When considering the utility of emerging nonsurgical options, Dr. Milad says that understanding their limitations is important. “Even with these new tools that we talked about, I will still consider them fertility unfriendly because [with] those treatments, you get ovulation suppression or ovulation inhibition [as the] mechanism of action, so you cannot pursue an attempt to get pregnant while on these agents,” says Dr. Milad. “We have a lot of options for patients that have symptomatic fibroids, but there’s definitely a gap in those therapies.”

### References

Drug duo boosts survival rate in endometrial cancer

Pembrolizumab plus lenvatinib induced a statistically significant and clinically meaningful improvement in overall survival, progression-free survival, and objective response rate compared with chemotherapy following prior systemic therapy in the phase 3 KEYNOTE-775/Study 309 trial.

Combining pembrolizumab (Keytruda) and lenvatinib (Lenvima) induced a statistically significant and clinically meaningful improvement in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) compared with chemotherapy as treatment of patients with advanced endometrial cancer after prior systemic therapy in the phase 3 KEYNOTE-775/Study 309 clinical trial (NCT03517449), according to a press release from Merck and Eisai, developers of the regimen.1

Based on these data, the companies plan to discuss the findings with regulatory authorities around the globe and intend to submit marketing authorization applications. The full data will be presented at an upcoming medical meeting.

“Women with advanced endometrial cancer are faced with high mortality rates and limited treatment options following initial systemic therapy,” said Gregory Lubiniecki, MD, an oncologist with Fox Chase Cancer Center, Temple Health, in Philadelphia, in a statement. “These are the first results from a phase 3 trial of a combination regimen including immunotherapy in advanced endometrial carcinoma that have shown a statistically significant improvement in OS, PFS, and ORR versus chemotherapy. Merck and Eisai are dedicated to continuing to research the pembrolizumab plus lenvatinib combination and discover new approaches to address unmet needs for devastating diseases such as endometrial carcinoma.”

The dual primary end points of OS and PFS, as well as the secondary efficacy end point of ORR, were achieved with the combination of the anti–PD-1 therapy and lenvatinib, an orally available multiple receptor tyrosine kinase inhibitor.

Investigators observed these positive results in both the mismatch proficient (pMMR) subgroup and the intention-to-treat (ITT) group, including both patients with endometrial cancer that is pMMR and those with microsatellite instability–high (MSI-H)/mismatch repair deficient (dMMR). The combination also appeared to have a safety profile consistent with prior findings for the regimen.

“We are encouraged by the data observed in KEYNOTE-775/Study 309, which represent a possible step forward for patients [affected] by advanced endometrial carcinoma and support the results seen in the advanced endometrial cancer cohort of KEYNOTE-146/Study 111,” stated Takashi Owa, vice president, chief medicine creation officer, and chief discovery officer of Eisai’s Oncology Business Group. “As more clinical data from the LEAP [Lenvatinib and Pembrolizumab] program are revealed, we cannot help but be energized by the trajectory of our collaboration with Merck and the benefits we hope to provide to patients together. Most importantly, we are grateful for the trust that the patients and health care professionals who participated in this trial have shown us.”

This article was originally published on Targeted Oncology.

For references, visit: contemporaryobgyn.net/view/drug-combination-shows-improved-survival-rate-in-patients-with-advanced-endometrial-cancer

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KEYNOTE-755/Study 309 is the confirmatory study for KEYNOTE-146/Study 111 (NCT02501096), which served as supportive data for the FDA’s 2019 accelerated approval of the combination regimen to treat patients with advanced endometrial carcinoma who are not MSI-H or dMMR, have disease progression following previous systemic therapy, and are not candidates for curative surgery or radiation therapy.

In KEYNOTE-146/Study 111, the ORR was 38.3% with the combination of lenvatinib and pembrolizumab per RECIST 1.1 criteria among patients with non–MSI-H/dMMR tumors. The complete and partial response rates, respectively, were 10.6% and 27.7%.2 The most common toxicities with the regimen included fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash.

To be included in the multicenter, open-label, randomized, phase 3 KEYNOTE-755/Study 309 trial, patients had to have a histologically confirmed diagnosis of endometrial carcinoma; documented evidence of advanced, recurrent, or metastatic disease; and radiographic evidence of disease progression 1 year following prior systemic chemotherapy.

They also had to have at least 1 measurable target lesion according to RECIST 1.1 and an ECOG performance status of 0 or 1. Patients were ineligible if they had carcinosarcoma, unstable central nervous system metastases, or an active malignancy other than endometrial cancer.

Additional secondary end points included health-related quality of life; number of patients with adverse events (AEs), with serious AEs, with immune-related AEs, and with treatment discontinuations due to AEs; and time to treatment failure due to treatment-emergent AEs. ■

WHO says pregnant women should not receive Moderna vaccine. The World Health Organization (WHO) has issued guidance recommending that pregnant women should not receive the Moderna Inc. vaccine unless the individual is at high risk of exposure or having a severe case.

Read the full story online at: contemporaryobgyn.net/WHOvaccine

IBD and Pregnancy CONTINUED FROM PAGE 22

IBD and Pregnancy

with the obstetrician to ensure an adequate fetal monitoring plan is in place prior to procedure.13

Mode of delivery

Despite higher rates of cesarean delivery in women with IBD compared with the general population, the only absolute contraindication to vaginal delivery is active perianal disease in women with Crohn’s disease.14 In women who have undergone J-pouch surgery and have done well, recent studies have shown no worsening of pouch function after a vaginal delivery, thus this decision can be individualized. The concern for vaginal delivery in women with IBD is the perceived increased risk of adverse outcomes with perineal lacerations, especially 3rd or 4th degrees, but thus far this has not been shown.15 Women with ileostomy or colostomy may also attempt a vaginal delivery if they have not had complications with their ostomies. Therefore, for the vast majority of women with IBD, there is no reason to recommend a planned cesarean delivery because of the IBD.

NSAIDS have been shown in IBD patients to cause ulcerations and flares.3 NSAIDS are also the most commonly used pain medication after delivery. Alternate forms of pain medications in IBD patients are preferred but if NSAIDS are required to control pain, we recommend using the lowest dose and shortest duration. Fenugreek is a common lactation supplement but should be avoided as it can cause bloody diarrhea and may precipitate postpartum flares in women with IBD.32 ■

FOR REFERENCES VISIT contemporaryobgyn.net/IBD
The Value of Hysteroscopy in the Diagnosis of Endometrial Cancer

Timely biopsy is essential to diagnosing endometrial cancer and identifying optimal treatment regimens. According to recent research, how does hysteroscopy compare to traditional, "blind" biopsies in terms of finding of positive peritoneal cytology, underdiagnosis, rate of 5-year recurrence-free survival, or rate of complications?

In this Contemporary OB/GYN® supplement, Dr. Yelena Havryliuk and Dr. Samar Nahas examine the findings of four key studies that demonstrate the effectiveness and unique utility of hysteroscopy.

Go to: contemporaryobgyn.net/view/better-for-women-series
Could this fetal demise have been averted?

Taking all facts into consideration, contemplate the course of action you would have taken under the circumstances presented here.

Factual Summary

Historically, the plaintiff, a G2P1, had difficulty getting pregnant and had intrauterine insemination (IUI) in 2013 and got pregnant on the first attempt. For that first pregnancy, the plaintiff treated with maternal fetal medicine specialist Defendant A for her prenatal care and delivered at defendant hospital via cesarean section due to decelerations and long labor.

With regard to the pregnancy to which this case relates, IUI alone was unsuccessful. The plaintiff became pregnant successfully after treatment with clomiphene after multiple attempts. After learning she was pregnant, the plaintiff transferred her care to Defendant A. Her first prenatal care appointment with Defendant A was on June 4, 2016. At this first appointment, they discussed the importance of getting her diabetes under control. The record indicated the plaintiff had a prior cesarean section and desired a vaginal birth after cesarean (VBAC). She continued care with Defendant A and her insulin levels were monitored very closely. An anatomy scan on July 20, 2016, showed fetus size equal to gestational date and there was no gross evidence of abnormalities. The prenatal record indicated in multiple places that the plaintiff desired a trial of labor after cesarean (TOLAC).

On September 28, 2016, the plaintiff signed a TOLAC form, which indicated a TOLAC delivery may have additional risks. The plaintiff had an uneventful prenatal course; throughout her scans, the size remained equal to dates; and there was good fetal movement. Given the plaintiff’s diabetes, she was scheduled for delivery at 38 weeks. The last prenatal visit prior to the delivery was December 7, 2016, at which time she was going to be evaluated for induction versus a repeat cesarean section.

At 3:22 AM on December 12, 2016, the plaintiff presented to the defendant hospital with complaints of contractions without a rupture of membranes. An exam was performed by the resident, which showed dilation of 1.5 cm and 90% effacement, with the membranes intact. It was decided to admit the plaintiff to labor and delivery, which was accomplished at 5:30 AM. At 6:43 AM, the next pelvic exam was performed, indicating the plaintiff was still at 1.5 cm dilation and 90% effacement. At 12:19 AM, a nonparty ob/gyn attending has a note that the plaintiff was informed of the nature of the delivery, including the risks and benefits of a VBAC versus performing a cesarean section. Pelvic exam revealed dilation to 3 cm and effacement at 90%. Artificial rupture of membranes produced clear fluid. Another pelvic exam was performed at 2:42 AM documenting 3.5 cm dilation with effacement still at 90%. The plaintiff was in latent labor and a decision was reached to perform an amnioinfusion to mitigate variable decelerations. Category 2 tracings were documented. At 5:16 PM, dilation was 4 cm, effacement of 90%, and there is a reference to continuing category 2 tracings. The plaintiff was in latent labor with variable...
decelerations that were not improving with amnioinfusion. If there was no change by 7 PM the plan was for a repeat cesarean section.

Defendant B, also a maternal fetal medicine specialist, came on as the covering attending and concurred with the plan. He also noted category 2 tracings, and his impression was a stable latent phase. The plan was still to have a vaginal delivery, but if there was no significant progress the plan would change to a repeat cesarean section. A 7:10 PM note indicated the plaintiff now wanted a cesarean section and at 7:37 PM there was a nonreassuring fetal heart tracing. The monitoring was discontinued and the plaintiff was taken to the operating room. The delivery was attended by Defendant B, and two defendant residents, along with nonparty resident.

The administration of anesthesia was started at 7:41 PM, with the skin incision at 7:53 PM, and the uterine incision at 8:21 PM. The time of delivery was recorded as 8:28 PM. The Apgar scores at delivery were 0 at 1, 5, and 10 minutes. The chart included a discrete certificate of spontaneous termination of pregnancy indicating this was a stillbirth and not a live birth with fetal demise shortly thereafter.

Defendant B’s operative note was written the following day at 2:54 PM. He noted the plan was that if the labor had not progressed, a cesarean section would be performed. The delivery was planned for shortly after 7 PM because of concerns regarding nonreassuring fetal heart tracings. Significantly, Defendant B noted dense adhesions after the abdominal incision, which was done over the prior uterine scar, and therefore additional assistance was requested.

He noted the skin incision was at 7:53 PM and the uterine incision was at 8:21 PM and the delivery effectuated at 8:28 PM.

**On September 28, 2016, the plaintiff signed a TOLAC form, which indicated a TOLAC delivery may have additional risks.**

Defendant C authored a note at 4:13 PM the following day and stated she was called into the operating room for assistance along with the nonparty resident. Her note stated the resident assisted with pushing the fetus from the vagina, but it was still difficult to deliver the infant, necessitating Defendant C to scrub in and deliver the fetal head, which she was unable to do on the first attempt. Defendant C’s note indicated she further extended the lower portion of the uterine incision in a T-fashion. Defendant D wrote an operative note two days later, stating she was called into the operating room after the fascia had been opened and extensive scar tissue was identified, with three discrete bands of muscular scar noted and the rectus muscle growing into the uterine myometrium. Defendant D noted that due to the close proximity of the bladder to the scar tissue and the uterus and the inability to clearly define planes between scar tissue and bladder, a retractor was placed to allow visualization of the lower uterus. The decision was made to place the uterine incision just above what was thought to be a window in the lower uterine segment, resulting in a transverse uterine incision, at which time the placenta was immediately encountered, and a cotyledon “popped out.” The placenta was noted to be dry and not bleeding, which Defendant D noted on interview was abnormal.

After the uterine excision was extended manually and attempts were made to deliver the fetus, Defendant D specifically noted help was called and it was noted it was very difficult to deliver the fetus. Defendant D noted that the incision was extended in a “T” fashion, which was performed by Defendant C. Per Defendant D’s note, the fetus was delivered cold, floppy, with no amniotic fluid or blood surrounding the fetus, with no blood in the umbilical cord. The mother–plaintiff was administered four units of blood and one unit of plasma due to uterine atony. Subsequently the plaintiff was seen by social workers and was able to spend time with the baby. A consent for an autopsy was signed. The plaintiff was very emotional and was ultimately discharged with a prescription for Xanax and was given a memory box. The autopsy report stated there was no obvious cause of death. The maternal diabetes was well controlled.

On January 24, 2017, the plaintiff had an ultrasound that showed a 4 cm clot in the uterus, which appeared to have retained placental tissue. On March 9, 2017, the plaintiff underwent a hysterosalpingogram that showed an enlarged uterine cavity with a defect occupying two-thirds of the cavity. This was suggestive of retained products of conception. The exam also showed that both tubes were visualized, and the left tube was freely...
AT 3:22 AM ON DECEMBER 12, 2016, THE PLAINTIFF PRESENTED TO THE DEFENDANT HOSPITAL WITH COMPLAINTS OF CONTRACTIONS WITHOUT A RUPTURE OF MEMBRANES.

well healed after she had her next menstrual cycle. On May 23, another hysterosalpingogram was performed that noted there was no longer a defect. The records indicate she was continuing to have thoughts of sadness and frustration and was struggling to be a present mother to her daughter while still continuing to grieve.

Allegations

Plaintiff argued that the 28 minutes it took to navigate down to the uterus, notwithstanding the presence of adhesions, was too long a period of time to comport with the standard of care and within that context the assistance of Defendant D should have been invoked before the approximate 8:13 PM summons to her, this after the initial skin incision at 7:53 PM. The more significant hurdle for the defense to overcome was the amount of time it took to extricate the fetus after the uterine incision (7 minutes). The plaintiff’s attorney alleged that the patient should not have been put through a trial of labor and the decision to perform cesarean delivery was negligently delayed.

Discovery

Records and deposition of the patient reflected that she and her family had undergone significant documented grief and trauma as a result of the fetal demise, leading to the dissolution of her marriage.

Defendant C testified that the fetal demise more likely than not occurred prior to the uterine incision and the 7-minute time interval necessary to extricate the fetus. Defendant C indicated that she was not privy to the extent of adhesions and scarring that were encountered initially by Defendant A and thereafter by Defendant D, but did indicate that based on her observation there was much scar tissue in the operative field and a lack of flexibility in the tissue. Additionally, although she did not participate in the uterine incision that was made by Defendant D, he described it as being in the lower uterine segment. The delivery report indicated that the fetus was delivered through the placenta, but the unified testimony of the defendants was that the placenta was not completely disrupted, but rather only a portion of the placenta, that is, a cotyledon was encountered. Although the delivery report does state that the fetus was delivered through the placenta, and that the placenta was completely disrupted for the 7-minute period it took to extricate the fetus, Defendant C testified that the placenta was not completely disrupted, and that the bleeding primarily was related to the uterine incision and the significant amount of adhesion dissection.

With regard to the labor and delivery, our expert indicated the decision to perform a cesarean section was timely made. The labor prior was latent on the precipice of converting to active labor. The fetal heart tracings never progressed to a Category 3 strip, which would have necessitated eminent delivery. The Category 2 strips required continuous monitoring. Our expert believed that it was within the standard of care for the physicians performing the cesarean section to perform a deliberate dissection of the adhesions given that this was not a stat or emergent cesarean section. It was appropriate to perform the cesarean section safely to avoid injury to maternal organs, including the colon and bladder. Our expert was supportive that the failure to progress, along with the fetal tachycardia and nonreassuring tracings, were a sign to do a cesarean section, but did not indicate
a stat cesarean section, and the fetal heart rate was not indicative of fetal distress.

With regard to the cesarean section itself, our expert was supportive of the deliberate nature of the dissection by the various physicians within the context of the nonemergent cesarean section, which would not have been the case if the fetus was in distress and a stat delivery was required. Our expert was supportive of the decision to perform a standard incision and not immediately utilize the “T” incision. The cesarean section was proceeding in a nonemergent way and as such, it was appropriate to want a small incision. There was difficulty delivering the fetus with the creation of the initial incision and there was still difficulty that necessitated a “T” incision, which was ultimately successful, but not timely enough to prevent the stillbirth. Our expert indicated that an earlier cesarean section would have been encumbered by the same difficulties as when it was ultimately performed, which would have still delayed the extrication of the fetus.

Result
The case settled as to defendant hospital.

Analysis
Plaintiffs’ counsel argued that the 28 minutes it took to navigate down to the uterus, notwithstanding the presence of adhesions, was too long a period of time to comport with the standard of care, and within that context the assistance of Defendant D should have been invoked earlier, but certainly before the approximate 8:13 PM summons after the 7:53 PM skin incision. The more significant hurdle for the defense to overcome in this case was the amount of time it took to extricate the fetus after the uterine incision, and it is anticipated that the practitioners would face much more vigorous cross-examination at trial before a lay jury concerning the interval steps that led to the uterine incision and the ultimate extrication of the fetus. Ultimately, given the hurdles posed by the alleged delay in extracting the fetus, and the inherent sympathy the prolonged delivery and result were likely to engender, the decision was made to settle the case on behalf of the hospital rather than risk a jury’s verdict.

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