BEYOND the PANDEMIC

A Guide to 14 Topics for Women’s Health
A PRESCRIPTION CONTRACEPTIVE THAT’S NON-HORMONAL AND USED IN THE MOMENT?

Discover pHirst in class

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REFERENCES:

• By maintaining the vagina’s acidic pH level, which reduces sperm motility and creates an inhospitable environment for sperm
• By creating a bioadhesive, viscous layer of gel over the vaginal and cervical surfaces, which allows Phexxi to remain in place and maintain an acidic environment within the vagina

HOW PHEXXI WORKS
• Phexxi is nonsystemic, and systemic exposure is not expected to lead to safety concerns
• Phexxi has no known contraindications or black box warning
• Phexxi is noncytotoxic
• Phexxi is easy to use, used in the moment, and easily reversible

WHY PHEXXI?

BASIC ACIDIC VAGINAL pH
3.5 /- 4.5

PH OF SEMEN
7.2 /- 8.0

Phexxi maintains the acidic vaginal pH (3.5-4.5) even in the presence of semen (7.2-8.0)

Watch this video to see for yourself how Phexxi works!

The Mechanism of Action of the Vaginal pH Modulator (VPM)
a Pharmacokinetic studies have not been performed.

Discover pHirst in class

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.

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 with history of recurrent urinary tract infection or urinary tract abnormalities.

ADVERSE REACTIONS
Most common adverse reactions were vulvovaginal burning sensation, pruritus, mycotic infection, genital discomfort (including male partners); urinary tract infection, bacterial vaginosis, vaginal discharge, and dysuria. Patients should consult their healthcare provider for severe or prolonged genital irritation or urinary tract symptoms.
Phexxi® is a vaginal pH modulator (VPM), a non-hormonal, prescription contraceptive that provides a different approach to daily contraception.

The Mechanism of Action of the Vaginal pH Modulator (VPM)

**HOW PHEXXI WORKS**

- By maintaining the vagina's acidic pH level, which reduces sperm motility and creates an inhospitable environment for sperm
- By creating a bioadhesive, viscous layer of gel over the vaginal and cervical surfaces, which allows Phexxi to remain in place and maintain an acidic environment within the vagina

**WHY PHEXXI?**

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- Phexxi is noncytotoxic
- Phexxi is easy to use, used in the moment, and easily reversible

Phexxi maintains the acidic vaginal pH (3.5-4.5) even in the presence of semen (7.2-8.0)

Advise the patient:
- To discontinue Phexxi if they develop a local hypersensitivity reaction.
- That Phexxi does not protect against HIV infection or other sexually transmitted infections.
- 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.

Please see full Prescribing Information for Phexxi. Please see Brief Summary on the following page.

REFERENCES:
PHEXXI® is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

INDICATIONS AND USAGE

PHEXXI® is indicated for the prevention of pregnancy in females of reproductive potential with suspected hypersensitivity to the ingredients in PHEXXI. Avoid PHEXXI use in females of reproductive potential with suspected hypersensitivity. Avoid PHEXXI use 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.

WARNINGS AND PRECAUTIONS

Cystitis and Pyelonephritis

Among 2804 subjects who received PHEXXI in Studies 1 and 2, 0.36% (n=10) reported adverse reactions of cystitis, pyelonephritis, or other upper urinary tract infection (UTI). 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

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of PHEXXI (pre-filled applicator with 5-gram dose) has been evaluated in two clinical trials (Study 1 and Study 2) in 2804 subjects (over 19,000 cycles of exposure). The racial/ethnic distribution was 66% White, 27% Black or African American, 2% Asian, 1% American Indian or Alaska Native, 0.3% Native Hawaiian or Pacific Islander, and 5% other; 32% of the study population was Hispanic. Study 1 included a one-year extension phase where 342 U.S. subjects were exposed to PHEXXI for 13 cycles.

Hypersensitivity Reaction:

Of the 2804 PHEXXI-treated subjects in Studies 1 and 2, one subject reported a suspected drug hypersensitivity. Avoid PHEXXI use in females of reproductive potential with suspected hypersensitivity to the ingredients in PHEXXI.

The most common adverse reactions (≥10%) in the U.S. population in Studies 1 and 2 (n = 2480) were: vulvovaginal burning sensation (18.0%) and vulvovaginal pruritus (14.5%). The majority of these adverse reactions were mild and few led to discontinuation. Table 1 summarizes the most common adverse reactions (≥2%) reported by subjects using PHEXXI in the U.S.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>(%)</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>

†Includes preferred terms (PT) vulvovaginal mycotic infection and vulvovaginal candidiasis.

‡Includes PTs urinary tract infection, streptococcal urinary tract infection, Escherichia urinary tract infection, and urinary tract infection bacterial.

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 human milk, the effects on the breastfed infant, or the effects on milk production.

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-menarchal 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.

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U.S. Patent 6,706,276

REFDOC-001013

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What’s New in Women’s Health?

The pandemic put all of us into survival mode. As the slow recovery begins, doctors have been able to bring to light other health topics from which attention was diverted during this time. That is the nature of this month’s cover story. Working with the Society of Academic Specialists in General Obstetrics and Gynecology, Editorial Board Member Christine R. Isaacs, MD, and William M. Leininger, MD, did a rigorous analysis to identify key areas of women’s health that underwent notable changes. The topics touch all areas of women’s health, including infertility, cervical cancer screening, emergency contraception, axillary adenopathy in patients with recent COVID-19 vaccinations, and intrapartum oxygen supplementation effects on Category II fetal monitoring.

The article is based upon Isaacs and Leininger’s co-presentation “While You Were Slee(PPE)ing: Women’s Health Updates Beyond the Pandemic’s Priorities” at the 2021 American College of Obstetricians and Gynecologists (ACOG) Annual Clinical and Scientific Meeting (ACSM). It is packed with resources. We took a slightly different tack with the article. Senior Editor Angie DeRosa compiled the information from ACOG and it went through review by Isaacs, Leininger, and Editor-in-Chief Catherine Y. Spong, MD. The information is very valuable and we would appreciate feedback on how you might use it in your practice. This article is complemented by several others based upon presentations at ACOG, including an update on CDC STI treatment guidelines; care considerations for pregnancy in transmasculine and non-binary patients; and insight into pregnancy and fertility apps. As with all conferences these days, this was held virtually. We all certainly hope that will not be the case for other conferences to be held later this year and into 2022 as we move beyond the pandemic.

For the obstetrical peer-reviewed article this month, David B. Nelson, MD, and Rachel Schell, MD, provide their expertise on Acute Fatty Liver of Pregnancy (AFLP). As they write, AFLP is a rare but potentially fatal condition characterized by hepatic failure. Typically, they say, it occurs in the third trimester of pregnancy. Because of differing study populations, the reported incidence varies from 1 in 7000 to 1 in 20,000 pregnancies. They include testing protocol for the evaluation of AFLP.

In this issue we also include another segment of Curbside Consults. These are articles with expert perspective from doctors in disciplines outside of ob/gyn that provide insight into conditions that can affect pregnant women. New Mother’s Thumb is covered by Jonathan E. Isaacs, MD, beginning on page 10. As he explains, De Quervain tenosynovitis, as it is medically known, is actually a misnomer since the condition lacks any true inflammatory component. But it is the clinical manifestation of stenotic changes to the tendon sheath surrounding the abductor pollicis longus and extensor pollicis brevis tendons as they pass over the radial styloid toward their insertion points at the base of the thumb metacarpal and the proximal phalanges, respectively.

Please provide feedback by email at COGEditorial@mmhgroup.com. We always want to know what articles you find valuable and what topics you would like to read about in future issues.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences™
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Beyond the Pandemic
A Guide to 14 Topics for Women’s Health

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When your mission is to eradicate cervical cancer...

You partner with the ones that will get you there—sooner.

Innovators are always looking forward, ready to find new solutions to existing challenges. That’s why Hologic and Google Cloud have combined forces to transform cervical cancer screening using the best minds in science and technology.

Together, we aim to evolve digital cytology through the Genius™ Digital Diagnostics System and enhance its deep learning-based AI. As our collective expertise continues to shape the way we screen for cervical cancer, and explores the potential impact on ovarian and endometrial cancers, we do so with a common goal in mind—to save more women’s lives.

* Genius Digital Diagnostics is CE-marked for diagnostic use in Europe and is not currently available for sale in the U.S. May not be available in all markets. Contact your local Hologic representative for availability in your country.

Google Cloud

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Attention and accountability are the 2 “A’s” that drive change. It’s true in medicine, business, even family. If it is not monitored, it is not regarded as important nor will change be affected. As ob/gyns, we see this in our practice. Those where cesarean delivery, open, and laparoscopic hysterectomy rates (among others) are publically known, ideally alongside others in similar practice, typically adjust if they become an outlier. Proving the point, several studies have shown that institutional interest in a metric directly affects change. Oshiro and colleagues demonstrated that implementing a policy and institutional awareness to reduce elective early-term deliveries affected an 83% decline in 1 year, from 37.8% to 4.8%.1 Wilson-Leedy and colleagues demonstrated a reduction in overall cesarean delivery rate and cesarean after induction of labor after implementing a labor management guideline at their institution.2 The key features are that leadership agrees the metric is important, it is tracked, and reported out regularly. Metrics that help guide decisions and ensure accountability are also useful. Without knowledge, we cannot affect change. In his 2015 book “Sapiens: A Brief History of Humankind,” Yuval Noah Harari wrote that knowledge is power.3 The real test of knowledge, he said, is not whether it is true, but whether it empowers us.

I can’t help but ask how we can use these concepts to enhance inclusion. I believe we can all find in our inbox invitations to meetings with expert panels—often with photos of the experts. Interestingly, and often, many experts seem to share similar characteristics. Although it is essential that those participating are considered experts—how do we ensure that we are truly expanding these rosters to represent the best cross-section?

When we developed a roster such as for a meeting, review group, or advisory panel at the National Institutes of Health, it was essential that the panel was diverse. Each roster was submitted with a table that listed the name, gender, race, ethnicity, and geographic location. These were attempts to ensure diversity. In my mind, this exercise is both positive and negative. On one hand, experts must be at the table, and people are not included simply on the basis of a characteristic. However, this method only ensures diversity and gives the appearance of being inclusive. Without directed thought to truly achieve real diversity, this method is not sufficient. It is critical to measure something meaningful, not just something easily measured. A difficulty in identifying diversity lies in the knowledge of who is creating the roster, who they know, and who is considered an expert in the topic. To enhance diversity, amplifying experts across gender, race, ethnicity, geography, and any other grouping is essential. A few groups have started this process. For example, there are lists of women in maternal and fetal health, microbiology, infectious diseases, cardiology, pelvic floor disorders, women’s health policy, and more, just as examples, that should be curated and then used to ensure representation. One such group is the Womxn’s Health Collaborative. At WomxnsHealthCollaborative.org/list-of-women-in-womens-health-research, you will find a working list of women in women’s health research. If you are so inclined, you should add your own name there and your areas of expertise. If you know of others who should be added, please also let them know.

Throughout human existence, the challenge has been putting new knowledge to work meaningfully as it is acquired in scientific research. We must continually assess where we are and where we want to be so that the knowledge we build upon becomes a true representation of the human race. Evolving science requires critical thinking for an effective model that will benefit human health. As physicians and scientists who dedicate our lives to women’s health, we should want that to be our legacy.

Catherine 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 cppong@mjhlfsciences.com

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* Actual patient comment from anonymous survey

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Society for Maternal-Fetal Medicine Consult Series #53
Intrahepatic Cholestasis of Pregnancy

by SOCIETY FOR MATERNAL-FETAL MEDICINE; RICHARD H. LEE, MD; MARA GREENBERG, MD; TORRI D. METZ, MD, MS; CHRISTIAN M. PETTKER, MD

Intrahepatic cholestasis of pregnancy (ICP) occurs in the second and third trimesters of pregnancy and is characterized by pruritus and elevated serum bile acid concentrations. Its incidence has been estimated to range from 0.3% to 15% in various populations, with most estimates from 0.3% to 0.5%. While ICP poses little risk for women, it does confer risk to the fetus. The persistence and intensity of associated pruritus are uncomfortable, and the increased risk of stillbirth is a significant concern to both patients and health care professionals.

What is the differential diagnosis of pruritus in pregnancy?
Pruritus is a common complaint in pregnancy. In ICP, itching is often generalized but predominantly affects the palms of the hands and the soles of the feet, is worse at night, and is generally not associated with a rash. The most frequent pathologic causes of pruritus specific to pregnancy include atopic eruption of pregnancy, polymorphic eruption of pregnancy, pemphigoid gestationis, and ICP.

How should a woman with pruritus in pregnancy be evaluated?
A detailed history and physical examination are imperative in making the diagnosis of ICP. In the process of taking the history and performing the physical examination, it is appropriate to consider and assess for other causes of pruritus without a rash (Box 1). ICP should be considered in a woman who develops new-onset pruritus without a rash in the second half of pregnancy.

In evaluating a patient for other potential causes for pruritus, one should assess the onset, extent, severity, aggravating and alleviating factors, timing, medical history, medications (eg, narcotics), allergies, past medical/family history of atopy (eg, eczema, allergic rhinitis, asthma), amount of bathing, household contacts, pets, and travel history. Sexual history and any history of intravenous drug use should be assessed to ascertain the patient’s risk of hepatitis and HIV. A history of ICP in any prior pregnancies should be assessed as well.

Other significant signs and symptoms to assess include recent changes...
in weight, appetite, skin or eye color (jaundice), and sleep habits. Excessive fatigue, insomnia, malaise, and abdominal pain and colic are not common with ICP. If present, evaluation for other causes of pruritus and hepatic disease may be warranted.

The physical examination should assess for the presence of rashes, excoriations, papules, plaques, or bullae. Although ICP is not associated with a rash, the intensity of the pruritus can lead to the development of excoriations or prurigo nodularis, which may be mistaken for a rash.4 Dark urine and jaundice are not common with ICP and suggest other hepatic diseases.

**Q** What laboratory evaluation is recommended for a pregnant woman with pruritus in whom ICP is suspected?

We recommend measurement of serum bile acid levels and liver transaminases in patients with suspected ICP (GRADE 1B). Mass spectrometry and liquid chromatography can evaluate for total and fractionated (cholic, chenodeoxycholic, and deoxycholic acid) bile acids. Total bile acids also can be assessed by enzymatic assay. Although the enzymatic assay does not provide fractionated bile acid levels, fractionated levels have limited utility, and the most clinically useful value is the total bile acid level.

The clinical diagnosis of ICP is based on pruritus symptoms and supported by the presence of elevated total serum bile acid levels and the absence of diseases associated with similar laboratory findings and symptoms. A serum total bile acid concentration of greater than 10 micromol/L often is used to diagnose ICP, although the data are limited and the diagnostic accuracy has been questioned.5,6 Increases in transaminases (eg, alanine aminotransferase and aspartate aminotransferase) can also sometimes be seen in ICP, although elevated transaminases are not necessary for the diagnosis. Although bile acid levels can be affected by a postprandial state, random bile acids can be used to diagnose ICP and are typically more convenient for the patient and practitioner than fasting bile acids. Box 2 lists other causes of ICP and elevated bile acid concentrations. Particularly in women with elevated bile acids before the second trimester of pregnancy, other etiologies should be considered.

**Q** Are particular women or populations at risk for ICP?

Women with preexisting hepatobiliary disease are reported to be at higher risk for ICP. Patients with a history of ICP are at risk for recurrence. ICP has been associated with multiple gestations and advanced maternal age, and familial clustering of cases of ICP also suggests a genetic component.1 ICP likely results from both environmental and hormonal influences in women who are genetically susceptible.

**Q** What are the complications of cholestasis of pregnancy?

ICP is associated with several adverse perinatal outcomes, including stillbirth, meconium-stained amniotic fluid, and preterm birth (both spontaneous and iatrogenic). Data suggest that the risk of stillbirth with ICP is associated with the total bile acid concentration,13 although some level of risk may still be present even with low bile acid concentrations. Women with ICP and bile acid levels ≥40 micromol/L have been reported to have increased risks of adverse perinatal outcomes, including preterm birth, asphyxia or respiratory distress syndrome, and meconium-stained amniotic fluid.14 Increased rates of both indicated and spontaneous preterm birth are reported with ICP, with the incidence of prematurity varying greatly among studies. Pregnancies complicated by spontaneous preterm birth have been reported to have an earlier onset of pruritus, and the prevalence of spontaneous preterm birth increases with higher total bile acid concentrations.15,16 There also is evidence that patients with ICP are at increased risk for preeclampsia.1

**Box 1. Pruritus Without Rash: Possible Causes**

- Chronic renal failure
- Drugs (hydrochlorothiazide, opioids, etc)
- HIV
- Hodgkin disease
- Hyperthyroidism
- Hypothyroidism
- Liver disease
- Malabsorption
- Multiple sclerosis
- Non-Hodgkin lymphoma
- Parasitosis/helminthosis
- Polycythemia rubra vera
- Psychiatric disease (eg, anxiety, depression, obsessive compulsive disorder)
- Tumors (paraneoplastic)

**Box 2. Other Etiologies**

- Drugs (hydrochlorothiazide, opioids, etc)
- HIV
- Hodgkin disease
- Hyperthyroidism
- Hypothyroidism
- Liver disease
- Malabsorption
- Multiple sclerosis
- Non-Hodgkin lymphoma
- Parasitosis/helminthosis
- Polycythemia rubra vera
- Psychiatric disease (eg, anxiety, depression, obsessive compulsive disorder)
- Tumors (paraneoplastic)
In patients with ICP, bile acid levels can increase during pregnancy and may increase rapidly near term. Given that higher serum total bile acid concentrations have been associated with adverse perinatal outcomes in some studies, repeat bile acid measurement has been suggested as potentially useful in guiding management. Follow-up laboratory testing may help guide delivery timing, especially in severe cases, but serial testing (eg, weekly) is not recommended.

Box 2. Other Causes of Elevated Bile Acids

- Autoimmune hepatitis
- Bacterial, fungal, and viral infections (eg, Epstein-Barr virus, cytomegalovirus)
- Cirrhosis
- Crohn disease
- Drug-induced cholestasis (related to trimethoprim-sulfamethoxazole, phenothiazines, ampicillin)
- Familial intrahepatic cholestasis
- Hepatic congestion from heart failure
- Hepatic amyloidosis
- Hepatic sarcoidosis
- Idiopathic adulthood ductopenia
- Liver tumor
- Lymphoma and solid organ malignancies
- Obstructive bile duct lesion
- Primary biliary cholangitis
- Primary sclerosing cholangitis (associated with inflammatory bowel disease)
- Sickle-cell intrahepatic cholestasis
- Total parental nutrition

ICP: intrahepatic cholestasis of pregnancy.

Is antepartum testing indicated for patients with ICP?

We suggest that patients with a diagnosis of ICP begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal fetal testing or at the time of diagnosis if the diagnosis is made later in gestation (GRADE 2C). The observed increased risk of stillbirth with ICP has prompted most practitioners to perform antenatal testing in this setting. However, the efficacy of antepartum fetal testing to prevent stillbirth in the setting of ICP is unknown. Several studies and case reports have reported stillbirth occurring within a few days of a reactive nonstress test.17-20 Antepartum fetal testing in ICP may not be useful because the mechanism of stillbirth is thought to be a sudden event rather than a chronic placental vascular process.

Recent clinical trials and meta-analyses support fetal surveillance with substantially lower rates of adverse perinatal outcomes compared with earlier reports, potentially due to more intensive monitoring with fetal surveillance and late-preterm or early-term delivery.11,14,21 The optimal frequency of testing is unknown and may be determined by criteria such as comorbidities or bile acid levels (eg, more frequent for total bile acid levels of 100 micromol/L or more). Due to the higher risk of stillbirth, patients with ICP should be placed on continuous fetal monitoring in labor.
When should women with a diagnosis of cholestasis be delivered?

While the risk for late stillbirth is avoided with an early planned delivery, this must be weighed against risks to the neonate related to prematurity. The timing of delivery should be approached using risk stratification based on patient-specific factors, including total bile acid levels, in a shared decision-making model. We recommend that patients with total bile acid levels ≥100 micromol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk for stillbirth increases substantially around this gestational age (GRADE 1B). We recommend delivery between 36 0/7 and 39 0/7 weeks of gestation for patients with intrahepatic cholestasis of pregnancy and total bile acid levels <100 micromol/L (GRADE 1C). Delivery timing for women with total bile acid levels <100 micromol/L should be individualized; it is reasonable for patients with bile acid levels of <40 micromol/L to be managed toward the later end of this time range, given the low risk for stillbirth seen in the studies referenced above, while women with total bile acid levels of ≥40 micromol/L should be considered for earlier delivery.

Delivery between 34 and 36 weeks of gestation can be considered in women with ICP, total bile acid levels of ≥100 micromol/L, and any of the following:

- excruciating and unremitting maternal pruritus not relieved with pharmacotherapy;
- a prior history of stillbirth before 36 weeks of gestation due to ICP with recurring ICP in the current pregnancy; or
- preexisting or acute hepatic disease with clinical or laboratory evidence of worsening hepatic function.

Any patient delivered for ICP prior to 36 weeks of gestation should be extensively counseled about the absence of definitive evidence that the maternal and fetal benefits of delivery outweigh the potential morbidity of prematurity. We recommend antenatal corticosteroids for fetal lung maturity for patients delivered before 37 0/7 weeks of gestation if not previously treated (GRADE 1A).

For patients with early-term pregnancies (37 to 38 weeks of gestation) with pruritis suggestive of ICP, no rash, and no bile acid results yet available to confirm the diagnosis, management should be based on shared decision-making that involves a discussion of the uncertainty of the diagnosis, the risks of ICP vs early-term delivery, and the values and

CONTINUED ON PAGE 45
IN THE TREATMENT OF VULVOVAGINAL CANDIDIASIS (VVC)

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At SCYNEXIS, we’re exploring the potential for a novel, non-azole treatment in VVC. Find out more at www.RETHINKVVC.com

References:

IF SHE'S GOING AROUND MORE THAN ONCE, IS IT TIME TO THINK TWICE ABOUT AZOLES?

For some patients, symptoms are not adequately addressed with 1 or 2 doses,2-4 and evidence suggests that broad and frequent use of azoles may be contributing to the increase in non-albicans Candida, and fluconazole-resistant Candida species.5-8

AS MANY AS 70% OF WOMEN HAVE BEEN PRESCRIBED FLUCONAZOLE BEYOND THE INDICATED 1-DOSE REGIMEN.1
IN THE TREATMENT OF VULVOVAGINAL CANDIDIASIS (VVC)

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At SCYNEXIS, we’re exploring the potential for a novel, non-azole treatment in VVC. Find out more at www.RETHINKVVC.com

US Women’s Sexual and Reproductive Health Trends

by SANDRA FYFE

Nearly a third of women in poor or fair health have been without health care during the COVID-19 pandemic. Even more worrisome, only half of uninsured women have been to an ob/gyn provider over the past 3 years. These findings are from the Kaiser Family Foundation’s (KFF) national 2020 Women’s Health Survey.

During a webinar, held on April 21, experts discussed the implications for practice and policy, how the pandemic is reshaping women’s sexual and reproductive health care, and how it will affect family planning and those who use it in the future.

The survey, which was conducted mainly online in English and Spanish from November 19 through December 17, included a sample of 3661 women aged 18 to 64 years along with a companion survey for 1144 men aged 18 to 64 years for results comparison. Women aged 18 to 49 years made up almost 74% of respondents (2695) and study authors said there was an oversample of respondents who were uninsured, Asian, and identified as lesbian. Researchers reported a margin of sampling error of +/-2% for the entire sample and higher in subgroups.

Overall Health

Usha Ranji, MS, associate director for women’s health policy at KFF, presented key findings on overall health. The survey revealed that many women have been without health care during the pandemic, with women in poor or fair health reporting the highest rates (23% for all women versus 32% for women in poor/fair health). This included skipping a medical test or treatment recommended by a provider and preventative services such as routine tests and yearly checkups (38% for all women versus 46% for women in poor/fair health). In comparison, 15% of men reported skipping treatments or tests and 26% missed routine services.

The pandemic brought an increase in telehealth use among women. However, telehealth was used less among uninsured and younger women. Most women gave their telehealth visits ratings of excellent or very good in the categories of mental health (90%), chronic illness management (91%), symptoms related to COVID-19 (90%), and annual wellness visits (89%).

Additionally, survey results revealed that the pandemic was responsible for women having trouble paying medical bills, with 26% reporting that COVID-19 was the reason for financial difficulty. Ranji explained that 42% reported preexisting financial difficulties and 31% reported preexisting difficulties and COVID as factors.

More than half (51%) of women reported that the pandemic has negatively affected their mental health compared with 34% of men. The rates were higher in mothers than in fathers (54% versus 35%, respectively). Negative mental health effects were highest among White women (54%) compared with Asian women (50%), Hispanic women (48%), and Black women (42%).

Many women have been without health care during the pandemic, with women in poor or fair health reporting the highest rates (23% for all women in poor/fair health).

Sexual Health, STIs, and Contraception

Questions on sexual and reproductive health were also asked in KFF’s survey. Brittani Frederiksen, PhD, MPH, senior policy analyst for women’s health policy at KFF explained that in the past 3 years, only 50% of uninsured women have visited an ob/gyn provider. Rates were higher for women on Medicaid (72%) and with private insurance (80%). Younger women aged 18 to 25 years...
were less likely to have visited a provider than women aged 26 to 34 years (79%) and women aged 35 to 49 years (76%). Black women were most likely to have visited a provider (78%) while Asian women (65%) were least likely. Seventy-three percent of White and Hispanic women visited a provider.

Most women had discussed contraception with their doctors (68%), but conversations on topics such as HIV (26%), other sexually transmitted infections, or STIs, (28%), and intimate partner violence (38%) were less likely brought up. White women (22%) were least likely to discuss HIV compared with Asian women (26%), Hispanic women (31%), and Black women (32%). For other STIs, White women once again had the lowest rates (25%), followed by Asian women (27%), Black women (30%), and Hispanic women (31%). Intimate partner violence was least discussed by Asian women (25%) followed by Black women (33%) and Hispanic and White women (40% each).

During the past year, 29% of women who were sexually active who did not use birth control reported a dislike of side effects or concern, Frederiksen explained. Twenty-three percent reported not wanting to use birth control; the same percentage said they did not mind if they got pregnant. Eleven percent said they did not think they could conceive. At least 1 method of birth control was used by 62% of women over the past year. Nearly 1 in 5 women were not using their preferred method of birth control, according to survey results, with 18% of women aged 18 to 49 years reporting that if any contraceptive method were available, they would want to use a different method than their current type. That number was highest among uninsured women (27%) followed by those on Medicaid (20%) and private insurance (16%). A quarter (25%) of women said the main reason they are not using their preferred method was because they could not afford the cost. Other reasons included their provider recommended a different type (20%), medical conditions that prevented the use of the preferred type (10%), the woman’s partner didn’t want her to use her preferred type (9%), or her preferred method was not available (8%). Twenty percent of women responded with reasons that were placed in an “other” category.

For women with private insurance, 20% paid out of pocket for the cost of contraception, Frederiksen said. Insurance covered the full cost for 64% of women and part of the cost for 21%. Five percent reported no coverage for birth control and 2% had insurance coverage but paid the entire cost themselves.

Overall, 65% of all women were comfortable with pharmacists prescribing contraception, and 70% were comfortable with making birth control available over the counter. Rates in these categories were higher in Democrats (72% and 78%, respectively) and Independents (63% and 70%, respectively) than Republicans (58% and 59%, respectively).

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

SOURCE
Acute Fatty Liver of Pregnancy

by David B. Nelson, MD and Rachel Schell, MD

Introduction
Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal condition characterized by hepatic failure. Typically, it occurs in the third trimester of pregnancy. Because of differing study populations, the reported incidence varies from 1 in 7000 to 1 in 20,000 pregnancies.1-4 The seriousness of this disorder is demonstrated by recent data from the U.S. Acute Liver Failure Study Group, which show that AFLP is the most common cause of acute liver failure during pregnancy—more common than drug-induced causes and hepatitis.5 Although AFLP shares some similar clinical and laboratory features with other obstetric medical complications—such as Hemolysis, Elevated Liver enzymes, and Low Platelet count syndrome (HELLP)—specific features can enable diagnosis. Management of this serious condition requires prompt recognition with close clinical surveillance following delivery. In this article, we will highlight these clinical management considerations and provide recommendations to facilitate care in women with AFLP.

Pathogenesis
The contemporary understanding of AFLP was established with the discovery of Reye syndrome in children during the 1960s, wherein deficiencies in mitochondrial enzymes were found to be responsible for fatty acid oxidation derangements.6 It is now understood that autosomal recessive mutations in genes that encode enzymes for the fatty acid metabolism pathway cause both the clinical features as well as histological microvesicular fatty hepatocyte infiltration seen in women with AFLP.7 During normal pregnancy, the fetal-placental unit metabolizes free fatty acids for fetal growth and development. Placental enzymes break down triglycerides into free fatty acids, which are then transferred to the fetus. When defects exist in the fatty acid oxidation pathway of the fetal-placental unit, the products—intermediate fatty acid metabolites—accumulate and enter the maternal circulation.8 These intermediate metabolites and associated reactive oxygen species are taken up by the maternal liver to cause microvesicular fatty infiltration, activate inflammatory processes, and cause cellular hepatic necrosis.9

Table 1. Symptoms of Acute Fatty Liver of Pregnancy

<table>
<thead>
<tr>
<th>Common symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Jaundice</td>
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<tr>
<td>Anorexia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Polyuria or polydipsia</td>
</tr>
<tr>
<td>Pruritis</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
</tbody>
</table>

Intermediate metabolites and associated reactive oxygen species are taken up by the maternal liver to cause microvesicular fatty infiltration, activate inflammatory processes, and cause cellular hepatic necrosis.

The mechanism leading to the accumulation of fatty acids and metabolites

David Nelson is chief of obstetrics and maternal medical director at Parkland Hospital in Dallas, Texas, and assistant professor of maternal-fetal medicine in the Department of Obstetrics & Gynecology at the University of Texas Southwestern Medical Center, also in Dallas.

Rachel Schell is a maternal-fetal medicine fellow at Parkland Hospital in Dallas, Texas, and an assistant instructor in the Department of Obstetrics & Gynecology at the University of Texas Southwestern Medical Center, also in Dallas.
in the maternal compartment involves 2 processes. First, the fetal-placental unit shares either a homozygous or compound heterozygous mutation resulting in an enzyme defect. Second, a heterozygous mother has a decreased ability to accomplish fatty acid oxidation in late pregnancy, leading to an inability to effectively clear the accumulating fatty acid metabolites that have been transferred from the deficient fetal-placental unit.

**Risk Factors**

The most prominent risk factors associated with AFLP include multifetal gestations, male fetus, and the aforementioned fetal fatty acid oxidation disorders. Although the majority of cases manifest in the third trimester, reported cases have occurred in the second trimester. Other risk factors include obesity, underlying metabolic disorders such as diabetes mellitus, and hepatic disorders such as intrahepatic cholestasis of pregnancy. Although there is a well-known association with preeclampsia, the direct cause and effect to AFLP is unclear. Because of the rarity of AFLP, clinical vigilance for associated symptomatology in all patients is paramount.

**Clinical Presentation and Evaluation**

The manifestations of AFLP range from minimal clinical findings and laboratory derangements to overt liver failure with hepatic encephalopathy. Common symptoms are listed in Table 1 and are often encountered in other obstetric “imitators,” such as HELLP syndrome, acetaminophen toxicity, and exacerbation of systemic lupus erythematosus. One of these clinical features—new-onset nausea and vomiting in the third trimester—is often associated with AFLP and merits further evaluation. The testing algorithm in Figure 1 can be used to facilitate assessment in women presenting with suspected AFLP. If clinical concern for AFLP remains high after initial laboratory evaluation, further confirmatory tests, also in Figure 1, can be obtained. These tests are readily available at most hospitals and focus on identifying hepatic and hematologic dysfunction, which are the hallmarks of AFLP.

To interpret the battery of laboratory tests used to diagnose AFLP, an understanding of the normal physiologic changes of pregnancy and their associated laboratory alterations is critical. “Normal values,” as referenced by an electronic medical record (EMR), often use reference ranges derived from males and/or nonpregnant women, which may be profoundly abnormal when referenced to the pregnant patient. For example, both serum cholesterol and plasma fibrinogen levels are significantly elevated in the third trimester of a normal pregnancy. Therefore, if levels of these analytes in pregnancy fall within the EMR reference range, they may actually be indicative of significant abnormality. Failure to recognize these differences may result in a missed diagnosis or unrecognized complication.

Classically, the Swansea criteria (Table 2) are used to confirm the diagnosis of AFLP. To meet the diagnosis of AFLP, 6 of the listed criteria must be met. These criteria are validated and effective; however, utilizing them requires the use of testing modalities that may not be readily available in all facilities. Moreover, some of these analytes require specific laboratory processing. For example, sampling for ammonia—an analyte elevated in hepatic dysfunction—can be influenced by transport of the sample on ice.

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**Table 2: Swansea Criteria for the Diagnosis of Acute Fatty Liver of Pregnancy**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Laboratory features</th>
<th>Ultrasonographic features</th>
<th>Histologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Bilirubin &gt;0.8 mg/dL</td>
<td>Ascites or echogenic liver</td>
<td>Microvesicular steatosis on liver biopsy</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Hypoglycemia &lt;72 mg/dL</td>
<td></td>
<td>AKI, ALT &gt;42 units/L</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>WBC &gt;11x10⁹/L</td>
<td></td>
<td>AST or ALT &gt;42 units/L</td>
</tr>
<tr>
<td>Polyuria or polydipsia</td>
<td>AST or ALT &gt;42 units/L</td>
<td></td>
<td>AKI or Cr &gt;1.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>AKI or Cr &gt;1.7 mg/dL</td>
<td></td>
<td>Coagulopathy or PT &gt;14 sec</td>
</tr>
<tr>
<td></td>
<td>Urine &gt;340 µmol/L</td>
<td></td>
<td>Ammonia &gt;47 µmol/L</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; ALT, alanine transaminase; AST, aspartate transaminase; Cr, creatinine; PT, prothrombin time; WBC, white blood cell count.
ultrasonographic findings are included in the Swansea criteria, the utility of such findings is limited. Imaging may still prove valuable for exploring the other common obstetric imitators previously mentioned. For example, a right upper quadrant ultrasound may be useful to diagnose a hepatic hematoma in the setting of HELLP syndrome. The use of liver biopsy was previously performed to diagnose AFLP, but given the challenges of such testing in a coagulopathic patient who has other features indicative of AFLP, it is rarely utilized today.

The laboratory abnormalities associated with AFLP demonstrate multi-organ injury, including hepatic, renal, and hematologic dysfunction. Hepatic dysfunction is characterized by liver damage with transaminase elevation, and by ineffective metabolic function as demonstrated by reduced production of cholesterol and fibrinogen. Renal impairment, caused by both intrinsic and prerenal insults, manifested as elevated serum creatinine—often greater than 1.0 mg/dL. Renal impairment, caused by both intrinsic and prerenal insults, manifested as elevated serum creatinine—often greater than 1.0 mg/dL. Associated hematologic abnormalities are frequently consistent with disseminated intravascular coagulation, characterized by prolonged clotting times, thrombocytopenia, hypofibrinogenemia, and elevated serum fibrin split products (D-dimer). There is often significant hemolysis, demonstrated by anemia and the presence of nucleated red blood cells.

These clinical and laboratory features can be useful in differentiating AFLP from HELLP syndrome. For example, patients with AFLP are more likely to present with nausea, vomiting, or jaundice. While hypertension is common to both diagnoses, it is present in only 70% of patients with AFLP and nearly all patients with HELLP syndrome.

Furthermore, AFLP is associated with significantly more hepatic and renal dysfunction as well as coagulopathy, demonstrated through lower fibrinogen levels (<300 mg/dL), lower total cholesterol (<150 mg/dL), higher total bilirubin (>1.0 mg/dL), and more significant renal dysfunction (Creatinine >1.0 mg/dL).

Management

The clinical management of the patient with AFLP relies on the following principles: (1) prompt recognition and evaluation of the mother and fetus; (2) planning for supportive care, such as reversal of coagulopathy; (3) preparation for delivery as soon as feasible; and (4) multidisciplinary care with anesthesiologists, intensivists, hepatologists, and pediatricians. Given the underlying pathophysiology of the disease, it is understood that liver damage will continue until the fetus is delivered.

After delivery, maternal recovery may be slow—lasting days to weeks—and often requires considerable supportive care. Any woman who presents with symptoms concerning for AFLP should be admitted to the labor and delivery unit of a hospital that has the ability to escalate care to an intensive care setting.

Once the patient is admitted, a number of simultaneous measures should be initiated in her care, beginning with close maternal and fetal monitoring. Two large-bore intravenous catheters are placed for maternal resuscitation. For women in whom a diagnosis of preeclampsia is being considered, magnesium sulfate infusion is initiated for eclampsia prophylaxis. In fact, concurrent preeclampsia is seen in approximately 70% of women with AFLP. Importantly, severe-range hypertension is treated with antihypertensive agents with a goal blood pressure of less than 160/110 mm Hg. Consultation with an anesthesiologist is imperative for maternal stabilization and in preparation for delivery. If the patient is encephalopathic or obtunded, airway protection is critical and may require endotracheal intubation. Placement of a nasogastric tube with administration of antacids to neutralize stomach contents may also be considered in patients with persistent nausea and vomiting.

Finally, consultation with the pediatric team is recommended for 2 reasons: (1) the need for neonatal resuscitation given the risks of fetal compromise; and (2) neonatal evaluation for metabolic derangements after delivery.

Delivery Considerations

Although delivery is required for the definitive treatment of AFLP, the diagnosis alone is not an indication for cesarean delivery. In fact, vaginal delivery is preferred given the proximity to severe coagulopathy in these patients. If vaginal delivery is pursued, vaginal trauma, such as episiotomy,
should be avoided. However, the cesarean delivery rate in women with AFLP is ultimately significant, as high as 67%, and is likely driven by fetal indications.

In the patient undergoing cesarean delivery, management of coagulopathy and preparation for excessive bleeding is critical. If the fetal status permits, coagulopathy should be corrected prior to proceeding with delivery. Hypofibrinogenemia should be corrected using fibrinogen-containing products—fresh frozen plasma or cryoprecipitate—with a goal fibrinogen level of at least 150 mg/dL. Similarly, thrombocytopenia should be corrected with the administration of platelets to a level greater than 50,000/mL. Despite preoperative resuscitation, the risk of intraoperative and postoperative bleeding remains significant. We recommend against the use of a Pfannenstiel incision and prefer a vertical midline skin incision at the time of cesarean delivery. This approach takes advantage of natural avascular surgical planes and allows for exploration of the upper abdomen if necessary. We have identified several cases of hematomas at the level of the rectus muscle in patients who received a Pfannenstiel incision in the setting of concurrent coagulopathy with AFLP. A surgical drain may be placed at the time of abdominal closure if there is ongoing surgical oozing or ascitic fluid within the abdomen; however, this is not our standard practice.

**Analgesia and Anesthesia**
Decisions regarding anesthesia and analgesia will also be influenced by metabolic and hematologic derangements. For women with mild coagulopathy and thrombocytopenia (platelets >70,000/mL), neuraxial anesthesia remains a reasonable option. However, reevaluation of laboratory indices may be necessary prior to removal of an epidural catheter as the nadir of coagulation studies and platelet count may worsen, and not recover, until several days postpartum. In more severe cases, general endotracheal anesthesia may be necessary for maternal airway protection, profound coagulopathy prohibiting regional anesthesia, or in the setting of fetal decompensation necessitating emergent cesarean delivery.

**Postpartum Recovery and Complications**
While delivery is the definitive treatment of AFLP, postpartum recovery may be prolonged and complicated by ongoing supportive care needs. Close surveillance and supportive care in either an intensive care unit or labor and delivery units are often necessary.
Serial measurements of hematologic, hepatic, and renal function should be performed every 6 to 12 hours for the first 1 to 2 days. Anemia is common during this time due to hemolysis or postpartum hemorrhage, and it frequently requires transfusion. Further, in patients with renal dysfunction who are receiving magnesium sulfate for seizure prophylaxis, serum magnesium levels should be monitored to avoid magnesium toxicity. Blood glucose levels should also be monitored hourly. If levels fall below 60 mg/dL, hypoglycemia should be treated with an infusion of 10% glucose.

Gradual recovery of laboratory analytes should be expected within a week following delivery. Hepatic dysfunction usually begins to improve 1 to 2 days after delivery. Transaminase levels decline linearly to levels of 100 units/L or less, and they may remain mildly elevated for several weeks. Other markers of hepatic dysfunction, including cholesterol and total bilirubin, begin improving after 3 to 4 days. Hemostatic dysfunction related to either liver synthetic function or consumptive coagulopathy improves over 4 to 6 days postpartum, as indicated by increasing plasma fibrinogen and declining D-dimer. The time course for recovery of aspartate transaminase and serum fibrinogen is shown in Figure 2. By contrast, renal recovery measured by serum creatinine may require 7 to 10 days. The postpartum course may be further complicated in some patients. Up to 15% of women with AFLP will develop pancreatitis. This is managed conservatively with intravenous hydration, analgesia, and nasogastric decompression. Transient diabetes insipidus may also be present, and excessive diuresis can be slowed using desmopressin in most cases.

Rarely, expected hepatic recovery does not occur, and persistent liver failure ensues. This requires management by hepatologists and intensivists and may involve the use of advanced therapies, such as plasma exchange or extracorporeal life-support systems. Transplantation may be necessary in patients with profound persistent hepatic failure with hypotension and acidosis. The need for transplantation is typically later in the recovery course and remote from delivery.

**Maternal and Perinatal Outcomes**

Together with advances in the diagnosis and management of AFLP, maternal and perinatal outcomes have significantly improved over the past 2 decades. Maternal mortality, which was as high as 80% to 90% in the 1980s, has now decreased to less than 10%. Perinatal mortality remains substantial and is now recorded in approximately 20% of AFLP cases. In a recent review of more than 350 women with AFLP, all survivors had full recovery of hepatic function. Despite these improvements, morbidity remains significant. With high rates of associated acute kidney injury, intensive care unit admission, and blood and component transfusion, most cases will trigger a severe maternal morbidity event. The recurrence of AFLP in a subsequent pregnancy is rare, but women who are heterozygous for a fatty acid oxidation enzyme defect are at increased risk. Therefore, screening for fatty acid oxidation disorders should be considered in women with a history of AFLP.

**Summary**

Once AFLP is identified, preparing for delivery and preparing for ongoing supportive maternal care postpartum are paramount. Key elements regarding the care of patients with AFLP are summarized in Table 3. Although AFLP is associated with maternal and infant morbidity and mortality, a multidisciplinary approach may be beneficial.

**FOR REFERENCES VISIT**
contemporaryobgyn.net/AFLP
Protect her possibilities with annual screening. Well woman exams have declined since the onset of the COVID-19 pandemic, and combined with the ongoing rise of STIs, this poses a serious threat to young women. Not only do women ages 15–24 account for 75% of chlamydia infections, but undiagnosed or untreated chlamydia and gonorrhea can lead to Pelvic Inflammatory Disease (PID) and cause infertility. So now is the time to protect her future.

Get her back to screening.


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Early and routine contraceptive counseling for all women of reproductive age with cardiovascular disease (CVD) or risk factors is an essential component of comprehensive cardiovascular care, according to evidence-based recommendations published in the Journal of the American College of Cardiology.

“This article is part of a 5-part series on cardio-obstetrics, aimed to provide practical guidance to cardiologists, obstetricians, and primary care physicians caring for reproductive-aged women with cardiovascular conditions,” said senior author Kathryn J. Lindley, MD, a cardiologist and an associate professor in the departments of medicine and obstetrics/gynecology at Washington University in St Louis, Missouri.

Lindley noted that the number of reproductive-aged women with underlying CVD is rising and that most of these women are sexually active.

The manuscript is particularly germane for contraception because cardiologists are not routinely trained on contraception and pregnancy planning during their fellowship, Lindley noted. “Unfortunately, few of these patients have discussed pregnancy planning and contraception with their cardiologist, and other patients have received inaccurate information,” she said. “Given the high rate of unplanned pregnancy, and the serious consequences to both mom and baby when a woman has underlying CVD, routine counseling on safe and effective contraception is essential.”

Due to the frequent care gaps during the transition from pediatric to adult cardiology care, “these conversations should begin in adolescence in pediatric cardiology clinics, then continue into adult cardiology clinics for women with congenital and acquired CVD alike,” Lindley stressed.

The article advocates multidisciplinary, patient-centered reproductive planning. “Due to the safety and efficacy of long-acting reversible contraception [LARC], the intrauterine device and subdermal implant are recommended for all women with underlying CVD and cardiovascular risk factors, including adolescents and nulliparous women,” Lindley said.

Barriers to access to contraception should also be considered for women with underlying CVD, including cost and pharmacy and clinic availability. “Multidisciplinary coordination is recommended to help overcome these challenges,” Lindley said. “It is probably not surprising to many that these conversations are not routinely taking place in cardiology clinics. In addition, some clinicians may be unaware of the excellent safety profile of LARC [methods] for women with CVD.”

However, ensuring that contraception counseling is a routine part of pediatric and adult cardiology clinic conversations “will require a shift in practice, and is compounded by barriers of time limitations in caring for complex patients,” said Lindley, who also is director of the Center for Women’s Heart Disease at Washington University. “I believe a key solution to these challenges is collaborative, multidisciplinary care between cardiology and obstetrics clinicians with cross-education.”

Lindley is excited and encouraged that reproductive planning and multidisciplinary pregnancy management for women with CVD is gaining traction. Because CVD is the major contributor of rising rates of maternal mortality in the United States, “ongoing education of both the cardiology and obstetrics/gynecology communities and their effective partnership will be paramount to continue to improve patient care,” Lindley said.

DISCLOSURES Lindley reports no relevant financial disclosures.

FOR REFERENCES VISIT contemporaryobgyn.net/cvd
Expert Perspectives:
A Discussion on TAP Blocks for Enhanced Recovery after Cesarean Delivery

In Enhanced Recovery for Cesarean Deliveries in the United States: Perspectives From the Frontlines – Part 2, a new print and digital supplement to Contemporary OB/GYN®, Stephen Garber, MD, addresses common challenges that can arise when starting a transversus abdominis plane (TAP) program that utilizes regional analgesia as part of an enhanced recovery after surgery protocol.

Dr. Garber also offers practical, implementable strategies—including how to incorporate training and secure buy-in from other stakeholders—and provides insights from his own experience.

Read the supplement now:
contemporaryobgyn.net/tap-program
Beyond the Pandemic

Significant updates occurred in women’s health issues while the world was in survival mode

Contemporary OB/GYN® Senior Editor Angie DeRosa compiled the following report based on a presentation at the 2021 American College of Obstetricians and Gynecologists (ACOG) Annual Clinical and Scientific Meeting (ACSM) by Editorial Board member Christine R. Isaacs, MD; and William M. Leininger, MD. Isaacs and Leininger presented the Kathryn M. and Thomas F. Purdon, MD, Generalists Session "While You Were Slei(PPE)ing: Women’s Health Updates Beyond the Pandemic’s Priorities" on May 2, the final day of the conference. It was a joint session of ACOG and the Society of Academic Specialists in General Obstetrics and Gynecology (SASGOG).
Isaacs and Leininger provided ACOG ACSM attendees with a high-level overview on clinically valuable updates that may have been pushed to the back burner as COVID-19-related medical care dominated 2020.1

Isaacs is an ob/gyn, a professor, academic specialist division chief, and medical director of midwifery services at the Virginia Commonwealth University School of Medicine in Richmond. Leininger is an ob/gyn at Naval Medical Center San Diego in California. He is an assistant professor of ob/gyn at the Uniformed Services University of Health Sciences in Bethesda, Maryland.

The actionable, direct patient care updates discussed by Isaacs and Leininger were published from late 2019 through 2020. However, during that time frame, many practice-based learning activities understandably focused on pandemic changes, and clinical practice was overwhelmed with pandemic adaptation and response activities. Their presentation identified high-value actionable updates for the generalist ob/gyn based on importance to one’s general clinical practice. Out of respect for content covered in other venues, they purposely chose focuses not related to COVID-19; diversity, equity, and inclusion; policy; and content identified in ACOG Practice Bulletins, Committee Opinions, Choose Wisely or in the Consult Series from the Society for Maternal Fetal Medicine (SMFM) all of which can be easily accessed by ACOG members. Isaacs and Leininger selected 30 articles of high value and interest that were screened based on title and abstract from multiple journals and health care organizations. The SASGOG board of directors reviewed and reprioritized the list to cover high volume and high consequence conditions. Isaacs and Leininger then selected the top 14 and summarized each.2 The SASGOG Board of Directors ultimately selected these articles to cover both high volume and high consequence conditions, Leininger said.

**Gonococcal Infection Treatment Guidelines**

The first topic involved updated guidelines from the Centers for Disease Control and Prevention (CDC) for uncomplicated cases of gonococcal infection.2 The guidelines recommend single agent treatment with ceftriaxone based on a person’s weight (500 mg intramuscular (IM) as a single dose for patients weighing 150 kg/–300 lb or less and 1 g intramuscularly for persons weighing 150 kg/–300 lb or more. These changes reflect the low incidence of ceftriaxone resistance and continued efforts at antimicrobial stewardship. The updated guidelines state that if chlamydia infection has not been excluded, providers should treat for such with doxycycline 100 mg orally twice per day for 7 days in a nonpregnant state or with azithromycin 1 g as a single dose during pregnancy.

The CDC has an app, STD Treatment (Tx) Guide, that can be downloaded from Apple’s App store or Google Play with the current updated guidelines.

**Hepatitis C Screening**

For hepatitis C virus infection in adolescents and adults, the US Preventive Services Task Force now recommends screening for all including pregnant and nonpregnant individuals.3 There is no vaccine, nor is pre- or postexposure prophylaxis available. The virus spreads primarily through parenteral exposure, blood, body fluids with blood, and injection drug use. The suggested practice change is to include hepatitis C antibody screening in new obstetric lab panels as this is often the first opportunity for patients to initiate health care and screening.

**Treating Couples with Unexplained Infertility**

In February 2020, the American Society for Reproductive Medicine published new practice guidelines for couples with unexplained infertility.1 These recommendations detail the evidence for various regimens using oral ovulation inducing medicines, gonadotropins, and intrauterine insemination (IUI) that have demonstrated little benefit for improving pregnancy rates or have a higher incidence of multiple gestations. Couples should start with 3 or 4 cycles of ovarian stimulation with oral agents and IUI. If that strategy is unsuccessful, then proceed to in vitro fertilization.
Umbilical Cord Milking vs Delayed Umbilical Cord Clamping
Isaacs and Leininger then moved on to an article that compared the risk of umbilical cord milking vs delayed umbilical cord clamping causing death or severe intraventricular hemorrhage (IVH) among preterm infants. The study was published in November 2019 in the *Journal of the American Medical Association*. It included 474 preterm infants (23 + 0 to 31 + 6 weeks gestational age [wGA]). An increased risk for severe IVH was found with umbilical cord milking, especially in 23 + 0 to 27 + 6 wGA ($P = .002$), they said. The practice implication is to prioritize delayed cord clamping over umbilical cord milking for placental transfusion at delivery of 23 + 0 to 27 + 6 wGA.

Cervical Cancer Screening
A major paradigm shift occurred following the American Society for Colposcopy and Cervical Pathology (ASCCP) updated guidelines for cervical cancer screening, Isaacs said. They moved it from relying on test results for algorithms to making it risk based, she added.

“The algorithms take into effect patients’ screening history,” Isaacs said. “Newer HPV infections are not as concerning as those that have existed and persisted.”

In addition, the American Cancer Society released recommendations in 2020 that endorsed and preferred primary HPV testing beginning at age 25. Then, in April 2021, ACOG released its practice advisory stating that screening should begin at age 21.

“We do not want to delay screening efforts,” Isaacs said. She added that for women of average risk, primary HPV screening is an option but not the only screening option. An updated app from ASCCP offers a tool for practicing ob/gyns to guide decision-making.

Withdrawing Approval of Makena
In October 2020, the Food and Drug Administration shared a summary of their deliberations to propose withdrawing approval of Makena, a drug that was approved for the prevention of recurrent preterm birth."Initial approval was accelerated because of the reduction in recurrent preterm birth. However, there was insufficient evidence at that time to evaluate newborn benefit. A subsequent study failed to find either newborn benefit or prolongation of pregnancy. Although a final decision on the proposal was still pending as of May 2, the date of Isaacs’ and Leininger’s presentation, clinicians will need to individualize complex issues for patients who are at risk of recurrent preterm delivery based on logistics, cost, utility, and expectation management. The experts recommended seeing recent releases from ACOG and SMFM on the meta-analysis from Evaluating Progestogens for Preventing Preterm Birth International Collaborative.

Levonorgestrel vs Copper IUD for Emergency Contraception
Next, Isaacs and Leininger covered a study that compared the use of the levonorgestrel vs the copper intrauterine devices (IUD) for emergency contraception. In January 2021, the *New England Journal of Medicine* published “Levonorgestrel vs Copper Intrauterine Devices for Emergency Contraception,” which involved 711 participants who were randomly assigned in a 1:1 ratio to receive a levonorgestrel 52-mg IUD or a copper T380A IUD for emergency contraception, with a 1-month follow up to assess for pregnancy. In the modified intention-to-treat and per-protocol analyses, pregnancy rates were 1 in 317 (0.3%; 95% CI, 0.01-1.7) in the levonorgestrel group and 0 in 321 (0%; 95% CI, 0-1.1) in the copper IUD group, indicating that the levonorgestrel IUD was noninferior to the copper IUD for emergency contraception. The study holds promise for future emergency contraception options and shared decision-making for patients.

Mifepristone Combination Therapy Compared with Misoprostol Monotherapy
Another important finding covered by Isaacs and Leininger involved a cost-benefit analysis of mifepristone plus misoprostol compared with misoprostol alone for the treatment of miscarriage. For their study published in *Obstetrics & Gynecology* in October 2020, investigators used decision tree analyses and Monte Carlo simulations covering variables such as medication costs, treatment success rates, need for surgery, and patient time away from work. Based on the parameters
used, the analysis results showed that combination therapy was consistently more cost-effective than monotherapy.

**Axillary Adenopathy in Patients with Recent COVID-19 Vaccination**

Recommendations also now exist for the management of axillary adenopathy in patients with recent COVID-19 vaccination from the Society for Breast Imaging. In normal screening mammograms, axillary adenopathy reports are 0.2% to 0.4%, which is rare, Isaacs and Leininger said. Lymphadenopathy as an unsolicited adverse event in vaccine trials was 1.1% based on clinical assessment. The true incidence is likely higher, they explained. The related practice change is the recommendation that breast screening imaging be performed prior to vaccination when possible. If mammographic screening is required after vaccination, consider postponing screening for at least 4 to 6 weeks after the final vaccination dose to avoid false-positive results. If a clinical breast concern exists, imaging should ensue without delay.

**Early-onset Breast Cancer Detection**

The presenters then addressed early-onset breast cancer—cases diagnosed in patients between ages 18 and 45 years—detection by discussing the CDC’s Bring Your Brave campaign, which shares patient stories and provides information for women affected by the disease, such as gaps and disparities in cancer diagnosis, treatment, and outcomes. Providers can take an evidence-based continuing medical education (CME)–accredited online course that reviews key concepts for early-onset breast cancer detection and/or reference “Executive Summary of the Early-Onset Breast Cancer Evidence Review Conference,” published in Obstetrics & Gynecology in June 2020. The series will continue with future topics (uterine, ovarian, vaginal, vulvar, and anal cancers), Isaacs explained, and she encouraged attendees to take the free CME course, offered through ACOG at acog.org.

**Intrapartum Oxygen Supplementation Effects on Category II Fetal Monitoring**

In a randomized controlled trial, published in the June 2020 issue of the American Journal of Obstetrics and Gynecology, investigators studied 114 term laboring patients randomized to room air versus 10L of oxygen per minute by face mask for Category II tracing. After 60 minutes, fetal heart tones were evaluated for recurrent/late variable decelerations, prolonged decelerations, tachycardia, and minimal variability, the presenters said. Investigators found that hyperoxia treatment does not appear to improve a Category II tracing. Therefore, based on this study and similar ones, clinicians should not delay other interventions while using oxygen supplementation for fetal in utero resuscitation, Leininger said.

**Indicators of Early Menopause Following Opportunistic Salpingectomy**

A cohort study from British Columbia, Canada, examined indicators of early menopause following opportunistic salpingectomy (OS). Investigators identified all women (41,413) who were 50 years or younger at the time of surgery who underwent OS from 2008 to 2014. For this cohort, they defined menopause onset as the age at the first visit for menopause symptoms or the first prescription for hormone therapy. They then allocated the patients by the following surgery types: hysterectomy alone, hysterectomy with OS, hysterectomy with bilateral salpingo-oophorectomy (BSO), tubal ligation, and OS for sterilization. Based on the study’s definition of menopause onset, only the women who underwent hysterectomy with BSO had an earlier age of onset of menopause.
compared with the other groups. These findings should help surgeons counsel patients about OS as a treatment option, according to Isaacs and Leininger.

**Vaginal Prep with Antiseptic Solution Before Cesarean for Preventing Postoperative Infections**

Isaacs and Leininger reviewed the Cochrane Library publication, which examined if vaginal preparations with antiseptic solutions done before cesarean delivery were effective in preventing postoperative infections such as endometritis and wound complications. The 21 trials that included 7038 women across 10 countries, Isaacs said. The antiseptics used were iodine-based or chlorhexidine solutions, as compared with saline or no vaginal cleansing. The results showed that use of vaginal antiseptic solutions probably did reduce the number of postoperative endometritis infections, wound infections, and fevers. The speakers concluded that this practice is a simple yet important intervention can have great benefit when incorporated into surgical checklists.

**Updated Maternity Care Standards**

The Joint Commission released updated maternity care standards for hypertension and hemorrhage effective January 1, 2021. It expands requirements for patient assessments, unit protocols and processes for patient management, equipment and supply access, recurring education and simulation drills, case reviews, and patient education. Based on discussions with other organizations and personal experience, the presenters said obstetric practices will need to pursue sustained, iterative, multidisciplinary effort over several months to fulfill these requirements.

**DISCLOSURES**

The views expressed by William Leininger, MD, are his own and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US government.

**FOR REFERENCES VISIT**

[contemporaryobgyn.net/beyondthepandemic](http://contemporaryobgyn.net/beyondthepandemic)

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**Women’s Health Updates Beyond the Pandemic**

**ARTICLES AND RESOURCES**

**UPDATED STRATEGIES FOR SELF-EDUCATION**

- Sign up for ACOG notifications and e-mails at: https://www.acog.org/myacog/communication-preferences

- Society for Maternal-Fetal Medicine updates: https://www.smfm.org/publications

- Other Specialty Societies have “Best Practices”, “Committee Opinions”, “Clinical Guidelines”, and similarly named summary documents.

- Choosing Wisely – search all medical specialty societies for their priority recommendations: https://www.choosingwisely.org/clinician-lists/

- CDC “Health Matters for Women” Newsletter sign-up: www.cdc.gov/women/newsletter/index.htm

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This list was compiled by Christine R. Isaacs, MD; and William M. Leininger, MD, as a supplement to their presentation from the 2021 ACOG Annual Clinical and Scientific Meeting, held virtually April 30-May 2.
An Update on CDC STI Treatment Guidelines

by GABRIELLE IENTILE
Assistant Editor, Drug Topics®

A session of the American College of Obstetricians and Gynecologists (ACOG) 2021 annual meeting pointed to the dramatic increase in STIs in the United States and presented highlights from the updated CDC STI guidelines.

Treatment guideline updates for sexually transmitted infection (STI) management in women were discussed in detail by experts during the 2021 American College of Obstetricians and Gynecologists (ACOG) Annual Clinical and Scientific Meeting, which was held virtually April 30 to May 2.

Kimberly A. Workowski, MD, FACP, FIDSA, professor of medicine in the Division of Infectious Diseases at Emory University in Atlanta, Georgia, and consultant to the Centers for Disease Control and Prevention (CDC) to coordinate development of the guidelines, described the clinical management of STIs in women, discussed appropriate diagnostic testing and new treatment recommendations, and highlighted evidence-based strategies aimed to address increases in gonorrhea, chlamydia, syphilis, and congenital syphilis.

“STIs are currently epidemic in the United States, and for the sixth year in a row, there’ve been dramatic increases in chlamydia, gonorrhea, and syphilis,” Workowski said. “About 1 in 5 [people] in the United States have an STD [sexually transmitted disease,] and it is a substantial amount of direct medical costs,” including nearly $16 billion each year for new STIs. In particular, congenital syphilis tripled between 2014 and 2018.

Myriad factors are at play regarding the high rates of STIs and hurdles to prevention, Workowski explained. Health disparities and the social determinants of health are primarily to blame and remain potent challenges in prevention. Stigma is also a significant barrier, fostering a lack of provider awareness, education, and training. The COVID-19 pandemic has been an added challenge in STI prevention; clinic closures, antimicrobial and swab shortages, and a focus on telehealth have set effective STI prevention back.

“There’s also limited point-of-care diagnostics [and] an increase in antimicrobial resistance. Our uptake of HPV vaccine has been suboptimal, and there’s also an ongoing syndemic of STI, HIV, viral hepatitis, and substance use disorder,” Workowski said.

The 2021 STD treatment guidelines are anticipated to be released by summer 2021, and Workowski’s presentation covered the highlights of the most recent updates. The guidelines in part focused on antimicrobial stewardship and emerging resistance, as well as updated treatment regimens and prevention recommendations for gonorrhea, chlamydia, trichomonas, and pelvic inflammatory disease.

Clinical Prevention Guidance

The first part of the updated guidelines focuses on clinical prevention guidance, including updates on:
- behavioral and biologic risk assessments;
- the importance of HPV vaccination;
- prevention methods, including condoms, circumcision, and emergency contraception;
- pre-exposure and post-exposure prophylaxis;
- multipurpose prevention technologies;
- retesting (chlamydia, gonorrhea, trichomonas) 3 months post therapy; and
- partner services.

Genital, Anal, or Perianal Ulcers

In the United States, herpes and syphilis are the most common infectious cause of ulcers. “These really differ depending on which geographic area and population that you serve,” Workowski said.

Specific evaluations include dark-field/syphilis serology, nucleic acid amplification for herpes, and herpes type specific serology. “Most clinicians don’t have the availability of dark-field, but we do have syphilis serology,” Workowski said.

Genital Herpes

Polymerase chain reaction (PCR) is the preferred diagnostic test for genital herpes, according to Workowski, but culture remains useful if a clinician suspects a patient may have acyclovir-resistant herpes.

Type-specific serologic testing is used in patients with recurrent genital lesions
with a negative PCR or culture, signs of infection but no lab test documenting herpes, and a partner with genital herpes. “The reason why the serologic testing is not commercially a universal recommendation is because there are problems with the specificity of the test, and there will be more specific language regarding serologic 2-step testing in terms of the confirmation of herpes,” Workowski said.

The guidance also has new sections on herpes simplex virus types 1 and 2 as well as hepatitis because of herpes.

**Syphilis**

Rising rates of syphilis have been seen over the past several decades. “What I really want to point out is the increase in the female rate, from about 2010 to the present,” Workowski said. “If we look at what’s happening, we really see the intersection of methamphetamine [and] heroin use associated with this increase in syphilis.”

There also has been a dramatic increase in congenital syphilis between 2010 and 2018.

- **Risk factors include:**
  - multiple partners,
  - sex with drug use or transactional sex,
  - late to prenatal care (after the second trimester) or no prenatal care,
  - methamphetamine/heroin use,
  - incarceration, and
  - unstable housing/homelessness.

There also is revised language that discusses reinfection or treatment failure, “really defined as a 4-fold increase in titer post treatment that’s sustained,” Workowski said.

As for syphilis treatment, Workowski explained that there are no changes, as investigators are still examining the role of enhanced therapy for patients who are not pregnant. A randomized clinical trial is working on addressing enhanced therapy.

REFERENCES

Workowski K. Sexually transmitted infections guidelines update. Presented at: The American College of Obstetricians and Gynecologists 2021 Annual Clinical and Scientific Meeting; April 30 to May 2, 2021; virtual.

The truth about pregnancy and fertility apps from ACOG 2021

**by LINDSEY CARR**

With nearly 2000 pregnancy and fertility apps available to mobile phone users, app overload and inaccuracy are major problems for ob/gyns and their patients. During the 2021 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting, 3 experts—Kathryn Marko, MD, NCMP; Katherine T. Chen, MD, MPH; and Tamika Auguste, MD—led presentations on these types of apps and remote monitoring, as well as the role they play in patient care.

Marko, who is the residency program director and assistant professor at the George Washington University in Washington, DC, discussed the good and bad aspects and future of mobile apps and remote monitoring. Through her work, she saw positive changes regarding smoking cessation and breastfeeding.
Care Considerations for Pregnancy in Transmasculine and Nonbinary Patients

by ANGIE DEROSA

If the oath “First, do no harm” is to be carried out by medical practitioners, one area in which this can truly be practiced involves the care of transmasculine or nonbinary patients who want to become pregnant or are already pregnant, according to a session from the 2021 American College of Obstetricians and Gynecologists (ACOG) Clinical and Scientific Meeting.

Elizabeth Cronin, MD, an assistant clinical professor of ob/gyn at Brown University/Women & Infants Hospital in Providence, Rhode Island, discussed care considerations for this population, providing attendees with ways to help create more welcoming environments, connect patients with local resources, and describe training considerations and best practices for serving them.

One of the best ways to do so is by understanding the following terms: sex, transgender, cisgender, and nonbinary. Sex, for example, is the presence of specific anatomy at birth that identifies biologically the male or female sex, Cronin explained. Gender is a social construct, she said; in transgender individuals, gender identity does not align with sex assigned at birth. In cisgender individuals, gender identity aligns with sex assigned at birth. Nonbinary refers to individuals who do not identify with either sex assigned at birth.

“The desire for pregnancy should always be discussed in presence of one’s gender identity,” Cronin said. “We need to be thinking about how we can provide the best care for all of our patients.”

Results of a 2015 survey, she explained, found that a quarter of individuals had reported they hadn’t seen a health care provider. It’s up to practitioners to educate themselves and understand barriers to care, insurance considerations, lack of staff or providers, and describe training considerations and best practices for serving them.

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Moderate-quality randomized control trials (RCTs), Marko said, led to improved smoking cessation with text message intervention (4 RCTs) that provided information on the risks to the mother and fetus in those who smoke. In addition, telehealth and text- and web-based interventions showed significant improvement in exclusive breastfeeding and breastfeeding continuation rates (3 RCTs). Vaccination rates, however, were not affected by telehealth interventions. No significant clinical or behavioral outcome related to pregnancy wellness, including healthy eating, physical activity, and maternal weight gain, was significantly changed by telehealth intervention with smartphone app and text messaging. “We can use this information to help patients more concretely connect with providers,” Marko said. “We can utilize this information to push out changes.”

App overload was highlighted by Chen, who compared the abundance of apps to a crowded flea market. “No one is telling you to seek out the yellow tent as the most accurate app. You don’t know to avoid the red tents,” Chen said. A major influx of available apps occurred from November 2013 to March 2021. For example, Chen explained, PubMed
individuals’ fear of being stigmatized, or being outed to employers, she said.

Preconception counseling is not going to be a whole lot different in these patients, Cronin said. Providers can begin by asking “Would you like to be pregnant within the next year?” and move the conversation forward from there. They can also have patients start prenatal vitamins and track cycles.

Individuals will need to consider if they have a partner whose sperm they can use or if donor sperm will be needed. The counseling of these patients can help them navigate this piece. In addition, patients should be counseled on potentially irreversible effects of hormonal therapies they are using and the effects on fertility.

The physician will have to discuss the length of time the patient will have to be off their testosterone hormones and set realistic expectations for achieving pregnancy. Providers also will want to consider helping people understand local parentage laws, available local resources, and financial considerations, such as local experts who may offer pro bono services.

Signage within facilities is also an important consideration. “Think about what you have up on the walls,” Cronin said. “What does your paperwork say? What do forms say? Are there things you can do to change your office setting so that it is more welcoming for all?”

When it comes to post partum, will the patient want to chestfeed or breastfeed? Word choice should be carefully considered for patient preference, Cronin advised. “Also talk with patients about options for chestfeeding if they do not get a sufficient supply,” she said. For example, have them reach out to local lactation specialists. Who is around who could be helpful and comfortable helping? She emphasized finding those people. The very practice of breastfeeding is gendered and women focused, so being sensitive about the needs of a transmasculine or nonbinary patient is crucial.

Psychological considerations must also be acknowledged throughout a transmasculine or nonbinary patient’s pregnancy experience, including lack of role models. A benefit of the COVID-19 pandemic is that a lot more resources have become available, especially online, Cronin said. She also explained the importance of making a patient feel safe and well cared for when they come to a hospital, since some patients have opted for home births because they feel safer.

And then there is postpartum depression: What resources exist? What about the physical effects to the patient? Providers can help patients navigate papers citing mobile apps went from 275 to 15,456 citations. Google’s search results went from 3.7 million to 1.63 billion results. Apps available on Apple’s App Store and Google Play went from 65,000 to 325,000. “A systematic process to identify and evaluate apps may help with the issues,” Chen concluded.

Auguste wrapped up the presentation with a focus on the gaps in mobile medical apps—namely, fertility awareness and fetal heart rate monitoring. Her first analysis was of Clue, an app that is marketed as a period and cycle tracker and ovulation calendar. Its website states, “The United States Food and Drug Administration (FDA) has classified Clue Birth Control as a software application that can be used as a contraception to prevent pregnancy.” However, the app was approved as a software application, not contraception. A disclaimer reads, “Note: Clue Period Tracker & Ovulation App should not be used as a contraceptive.” Auguste emphasized the importance of communicating this information to patients. It is crucial for providers to “know what’s out there and know the data,” Auguste said. “Patients are going to use these apps.”

REFERENCE

Marko K, Chen KT, and Auguste T. Mobile apps in obstetrics and gynecology: The good, the bad, and the ugly. Presented at: 2021 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting; April 30 to May 2, 2021; virtual.
potential issues and concerns.

Abortion services should also be evaluated. Statistically speaking, unwanted pregnancies track with this population similarly to that of the general population, Cronin said. “What would it be like to obtain abortion care for someone who doesn’t identify as a woman?” she asked.

To address the needs of the transmasculine and nonbinary patient population, providers can consistently train staff. “How can I make a restroom that is gender neutral?” Cronin asked. “Take a walk through your spaces. How gendered is my labor room? We can make sure that everyone feels more welcome in our spaces.”

Cronin used a personal example involving an incident with front desk staff, which reminded her that training is an ongoing process. “Patients can get all the way to your exam room, and if they have been misgendered and felt isolated, no one is going to want to come back to your office,” she said.

One session participant offered a list of best practices: Create and follow a protocol for noting chosen names and pronouns; have clear lines of referral for questions; select a point staff person to provide guidance and assistance with procedures; offer referrals to other trans-competent and safe providers of myriad services and complaints; take accountability for trans-negative responses; provide ongoing training and retraining, as needed; and lead by example in all cases.

REFERENCE
Cronin E. Care considerations for pregnancy in transmasculine and nonbinary patients. Presented at: 2021 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting; April 30 to May 2, 2021; virtual.

Women’s Health Updates Beyond the Pandemic

ARTICLES AND RESOURCES

Update to CDC’s Treatment Guidelines for Gonococcal Infection, 2020
SUMMARY: New treatment guidelines for gonococcal infection and clarification on concurrent treatment for chlamydia.

Screening for Hepatitis C Virus (HCV) Infection in Adolescents and Adults US Preventive Services Task Force Recommendation Statement
JAMA. 2020;323(10):970-975
SUMMARY: All pregnant persons should be screened for HCV during each pregnancy, except in settings where the prevalence of HCV infection is less than 0.1%.

Withdrawing Approval of Makena — A Proposal from the FDA Center for Drug Evaluation and Research
N Engl J Med 383:24
SUMMARY: FDA summary of the reasoning in this proposal, based on results in the follow-up studies that did not find treatment led to prolongation of pregnancy nor that it provided newborn benefit.

Evidence Based Tx’s for Couples with Unexplained Infertility: A Guideline
Fertil Steril 2020 Feb;113(2):305-322.
SUMMARY: Evidence-based guidelines on effective and ineffective treatments; reasonable to provide 3-4 cycles of clomiphene citrate or letrozole ovulatory stimulation with timed IUI, then refer for IVF if no pregnancies.

2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors
J Low Genit Tract Dis 2020;24: 102–131
SUMMARY: New management guidelines and app that shifts from test result-based recommendations to risk-based recommendations.

Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception
N Engl J Med 2021;384:335-44. DOI: 10.1056/NEJMoa2022141
SUMMARY: LNG-IUS is non-inferior to copper IUD for emergency contraception.

Read the complete list online at contemporaryobgyn.net/whubtp

This list was compiled by Christine R. Isaacs, MD; and William M. Leininger, MD, as a supplement to their presentation from the 2021 ACOG Annual Clinical and Scientific Meeting, held virtually April 30-May 2.
IMPORTANT SAFETY INFORMATION FOR NEXTSTELLIS®
(drospirenone and estetrol tablets 3 mg/14.2 mg)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEXTSTELLIS safely and effectively. See full prescribing information for NEXTSTELLIS.

NEXTSTELLIS (drospirenone and estetrol tablets), for oral use
Initial U.S. Approval: 2021

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 NEXTSTELLIS
• Cigarette smoking increases the risk of serious
cardiovascular events from combination oral
contraceptive (COC) use.

INDICATIONS AND USAGE
NEXTSTELLIS is a combination of drospirenone, a progestin,
and estetrol, an estrogen, indicated for use by females of
reproductive potential to prevent pregnancy.

Limitations of Use
NEXTSTELLIS may be less effective in females with a BMI
≥30 kg/m². In females with BMI ≥30 kg/m², decreasing
effectiveness may be associated with increasing BMI.

DOSE AND ADMINISTRATION
• Take one tablet by mouth at the same time every day.
• Take tablets in the order directed on the blister pack.

DOSE FORMS AND STRENGTHS
NEXTSTELLIS consists of 28 tablets in the following order:
• 24 pink active tablets each containing drospirenone
3 mg and estetrol 14.2 mg
• 4 white inert tablets

CONTRAINDICATIONS
• A high risk of arterial or venous thrombotic diseases
• Current or history of a hormonally-sensitive malignancy
(e.g., breast cancer)
• Hepatic adenoma, hepatocellular carcinoma, acute
hepatitis or decompensated cirrhosis
• Co-administration with hepatitis C drug combinations
containing ombitasvir/paritaprevir/ritonavir, with or
without dasabuvir
• Abnormal uterine bleeding that has an undiagnosed
etiology
• Renal impairment
• Adrenal insufficiency

WARNINGS AND PRECAUTIONS
• Thromboembolic Disorders and Other Vascular Problems:
Stop NEXTSTELLIS if a thrombotic or thromboembolic
event occurs. Start no earlier than 4 weeks after delivery.
Consider all cardiovascular risk factors before initiating
in any female, particularly in the presence of multiple
risk factors.
• Migraine: Discontinue if new, recurrent, persistent,
or severe migraines occur.
• Hormonally-Sensitive Malignancy: Discontinue
NEXTSTELLIS if a hormonally-sensitive malignancy
is diagnosed.
• Liver Disease: Withhold or permanently discontinue for
persistent or significant elevation of liver enzymes.
• Glucose Tolerance and Hypertriglyceridemia: Monitor
glucose in females with prediabetes or diabetes. Consider
an alternate contraceptive method for females with
hypertriglyceridemia.
• Gallbladder Disease and Cholestasis: Consider
discontinuing NEXTSTELLIS in females with symptomatic
gallbladder or cholestatic disease.
• Bleeding Irregularities and Amenorrhea: May cause
irregular bleeding or amenorrhea. Evaluate for other
causes if symptoms persist.

ADVERSE REACTIONS
Most common adverse reactions (≥2%): bleeding
irregularities, mood disturbance, headache, breast
symptoms, dysmenorrhea, acne, weight increased,
and libido decreased

DRUG INTERACTIONS
• CYP3A Inducers: May lead to contraceptive failure and/or
increase breakthrough bleeding. Avoid concomitant use.
If concomitant use is unavoidable, use an alternative or
back-up contraceptive method during co-administration
and up to 28 days after discontinuation of the CYP3A
inducer.
• See Full Prescribing Information for additional clinically
significant drug interactions.

USE IN SPECIFIC POPULATIONS
• Pregnancy: Discontinue if pregnancy occurs.
• Lactation: Advise postpartum females that NEXTSTELLIS
can decrease milk production.

To report SUSPECTED ADVERSE REACTIONS,
contact Mayne Pharma at 1-844-825-8500 or FDA
at 1-800-FDA-1088 or www.fda.gov/medwatch


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The first and only pill to contain estetrol (E4)—a native human estrogen, now produced from a plant source, combined with the proven progestin drospirenone

**NEXTSTELLIS** demonstrated efficacy and safety in 2 Phase III studies of 3632 patients including:

- A broad age range of women (16-50 years of age)
- A racially diverse patient population (83% white, 11% black, 3% Asian, and 3% other)
- Women with higher BMI (23% had BMI 30-35 kg/m²)

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**E4** Introducing estetrol—the estrogen that makes NEXTSTELLIS unique

- A naturally occurring human estrogen
- Unique pharmacologic profile, including a long half-life (24-28 hours)
- Selective actions on estrogen receptors—the first estrogen to be described as a **NEST**: a Native Estrogen with Selective actions in Tissues
- Minimally metabolized by the liver

**Contraceptive efficacy in patients with BMI up to 35 kg/m²**

- 98% effectiveness in preventing pregnancy with a 24/4 monophasic regimen (Pearl index: 2.65)
- The high BMI subgroup (BMI 30-35 kg/m²) had a Pearl index of 2.94

**Bleeding pattern similar to a natural, predictable cycle**

- Low rates of unscheduled bleeding and spotting even in cycle
- 85% of women experienced regular withdrawal bleeding

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*Based on data from nonclinical pharmacology studies.
†From a Phase III, open-label, single-arm study (N=1524) in women 16 to 35 years of age with 12,763 at-risk cycles.
‡The Pearl index is the FDA-required measure of efficacy for a birth control method and is calculated based on the number of patients, at-risk cycles, and unintended pregnancies during the study.
BMI=body mass index.
Warning: Cigarette Smoking and Serious Cardiovascular Events

Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive (CHC) use. This risk increases with age, particularly in females over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NEXTSTELLIS, are contraindicated in females who are over 35 years of age and smoke. [See Contraindications and Warnings and Precautions]

Indications and Usage

NEXTSTELLIS is indicated for use by females of reproductive potential to prevent pregnancy. Limitations of Use

NEXTSTELLIS may be less effective in females with a BMI ≥ 30 kg/m². In females with BMI > 30 kg/m², decreasing effectiveness may be associated with increasing BMI [see Clinical Studies]

Dosage and Administration

Additional Administration Information

Starting NEXTSTELLIS in females with no current use of hormonal contraception

Important:

- In females with irregular menstrual cycles, pregnancy testing may be necessary prior to initiation of this product.

Day 1 Start:

- Take the first pink active tablet on the first day of menses.
- Take subsequent pink active tablets once daily at the same time each day for a total of 24 days.
- Take one white inert tablet daily for 4 days and at the same time of day that active tablets were taken.
- Begin each subsequent 28-day pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)

If not starting on the first day of menses, use a non-hormonal contraceptive (e.g. condoms and/or spermicide) as back-up until one active tablet has been taken daily for 7 days in a row.

Contraindications

NEXTSTELLIS is contraindicated in females who develop or are known to have the following conditions:

- A history of, increased risk for, or current arterial or venous thrombotic/thromboembolic diseases. Examples include females who are known to:
  - Have cerebrovascular disease [see Warnings and Precautions]
  - Have coronary artery disease [see Warnings and Precautions]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions]
  - Have inherited or acquired hypercoagulopathies [see Warnings and Precautions]
  - Have uncontrolled hypertension or hypertension with vascular damage [see Warnings and Precautions]
  - Have diabetes mellitus with hypertension or end-organ damage; or diabetes mellitus of > 20 years duration [see Warnings and Precautions]
  - Have migraine headaches with aura [see Warnings and Precautions]
  - Current or history of a hormonally-sensitive malignancy (e.g. breast cancer) [see Warnings and Precautions]
  - Hepatic adenoma, hepatocellular carcinoma, acute hepatitis, or severe (decompensated) cirrhosis [see Warnings and Precautions]
  - Use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [see Warnings and Precautions]
  - Abnormal uterine bleeding that has an undiagnosed etiology [see Warnings and Precautions]
  - Renal impairment [see Warnings and Precautions]
  - Adrenal insufficiency [see Warnings and Precautions]

Warnings and Precautions

Thromboembolic Disorders and Other Vascular Problems

- Stop NEXTSTELLIS if an arterial or venous thrombotic/thromboembolic event occurs.
- NextSTELLIS if there is unexplained loss of vision, protonotosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue NEXTSTELLIS during prolonged immobilization.
- Start NEXTSTELLIS no earlier than 4 weeks after delivery in females who are not breast feeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week. Before starting NEXTSTELLIS, evaluate any past medical history of or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. NEXTSTELLIS is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases [see Contraindications].

Cardiovascular and Cerebrovascular Events

Use of CHCs increases the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among females over 40, smokers, and females with hypertension, dyslipidemia, diabetes, or obesity. The risk increases with age, particularly in females 35 years of age and older, and with the number of cigarettes smoked. In addition to cigarettes, use of other nicotine-containing products – including cigars, smokeless tobacco, hookah tobacco, e-cigarettes, and nicotine replacement therapy – may also increase the risk of serious cardiovascular events from CHC use.

Venous Thromboembolism

Use of CHCs also increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. The rate of VTE in females using COCs has been estimated to be 3 to 9 cases per 10,000 woman-years and should be considered in the context of other female of reproductive potential subpopulations who are not taking CHCs [see Adverse Reactions]. Risk factors for VTEs include smoking, obesity, family history of VTE, and prolonged immobilization in addition to other factors that contraindicate use of CHCs [see Contraindications]. The presence of multiple risk factors for VTE may increase the risk synergistically. The risk of VTE is highest during the first year of CHC use and when restarting hormonal contraception after a break of four weeks or longer. The risk of VTE returns to baseline approximately 3 months after CHC use is discontinued.

Postpartum Venous Thromboembolism

The risk of VTE is increased during the first six weeks postpartum compared to the risk in non-pregnant, non-postpartum females. The risk is highest in the first three weeks postpartum, but remains higher than baseline until at least six weeks postpartum. The presence of multiple risk factors for VTE may further increase the risk. Obstetric complications may extend the elevated risk up to 12 weeks postpartum.

Figure 1 shows the risk of developing a VTE for females who are not
of age, seven subjects were noted to have hyperkalemia and one subject discontinued due to elevated potassium levels. Most females who developed hyperkalemia in the clinical development studies of NEXTSTELLIS had only mild potassium elevations and/or isolated increases that returned to normal while still on study medication.

**Hypertension**

NEXTSTELLIS is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease [see Contraindications]. For all females, including those with well-controlled hypertension, monitor blood pressure periodically and stop NEXTSTELLIS if blood pressure rises significantly. An increase in blood pressure has been reported in females using COCs. This increase is more likely in older females with extended duration of use.

**Migraine**

NEXTSTELLIS is contraindicated in females who have migraines with aura [see Contraindications]. Discontinue NEXTSTELLIS in females using NEXTSTELLIS who develop new migraines that are recurrent, persistent, or severe. Discontinue NEXTSTELLIS if there is an increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event). Migraines with aura increase the risk for stroke. This stroke risk is further increased in females who have migraines with aura with use of CHCs.

**Hormonally-Sensitive Malignancies**

NEXTSTELLIS is contraindicated in females with current or a history of hormonally-sensitive malignancies (e.g., breast cancer) [see Contraindications]. Discontinue NEXTSTELLIS if a hormonally-sensitive malignancy is diagnosed. NEXTSTELLIS may promote growth of any hormone receptor-positive tumor, both within and external to the female reproductive tract. Examples of tumors external to the female reproductive tract that may be hormone receptor-positive include melanoma, adenocarcinoma of the lung, and meningioma.

**Liver Disease**

**Elevated Liver Enzymes**

NEXTSTELLIS is contraindicated in females with acute hepatitis or severe (decompensated) cirrhosis [see Contraindications]. Withhold or permanently discontinue NEXTSTELLIS for persistent or significant elevation of liver enzymes. NEXTSTELLIS can cause elevated liver enzymes.

**Liver Tumors**

NEXTSTELLIS is contraindicated in females with hepatic adenomas and malignant liver tumors [see Contraindications]. CHCs increase the risk of hepatic tumors, particularly hepatic adenomas. Rupture of hepatic adenomas may cause death from abdominal hemorrhage.

**Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**

CHCs, such as NEXTSTELLIS, are contraindicated for use with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) [see Contraindications]. Discontinue NEXTSTELLIS prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir (with or without dasabuvir). NEXTSTELLIS can be restarted approximately 2 weeks following completion of treatment with this Hepatitis C combination drug regimen. During clinical trials with the above-mentioned Hepatitis C combination drug regimen, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in females using ethinyl estradiol (EE)-containing drugs, such as CHCs. Females using medications containing estrogens other than EE had a rate of ALT elevation similar to those not receiving any estrogens. NEXTSTELLIS contains EE rather than EE, but as no data are available for co-administration with this Hepatitis C combination drug regimen, caution is warranted.

**Glucose Tolerance and Hypertriglyceridemia**

**Glucose Tolerance**

Carefully monitor females with prediabetes and diabetes who are using NEXTSTELLIS. NEXTSTELLIS may decrease glucose tolerance [see Clinical Pharmacology].

**Hypertriglyceridemia**

Consider alternative contraception for females with hypertriglyceridemia. Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using NEXTSTELLIS, which may increase the risk of pancreatitis.

**Gallbladder Disease and Cholestasis**

Consider discontinuing NEXTSTELLIS in females with symptomatic gallbladder disease or cholestatic disease. Studies suggest an increased risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Females with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

**Effect on Binding Globulins**

Increase the dosage of thyroid hormone replacement therapy as needed in females taking NEXTSTELLIS [see Clinical Pharmacology]. The estrogen component of NEXTSTELLIS may
increase the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin.

**Bleeding Irregularities and Amenorrhea**

**Unscheduled Bleeding and Spotting**

Females using NEXTSTELLIS may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first 4 months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy. Unscheduled bleeding was defined as bleeding or spotting that occurred on Day 4 through Day 24 of a 28-day cycle. Based on subject diaries from C302 (US/CA), the proportion of subjects reporting unscheduled bleeding or spotting per 28-day cycle decreased over time: 30.3% at Cycle 1 versus 17.4% at Cycle 12. The mean number of unscheduled bleeding/spotting days per cycle also gradually decreased over time, with a mean of 0.4 (± 1.42) bleeding days at Cycle 1, versus a mean of 0.2 (± 0.98) bleeding days at Cycle 12. Absence of Scheduled Bleeding

Females who use NEXTSTELLIS may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant [See Adverse Reactions]. The proportion of subjects reporting absence of scheduled bleeding remained constant overall, with on average 15.5% of subjects reporting absence of scheduled bleeding from Cycles 1 through 12.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than prescribed), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. After discontinuation of NEXTSTELLIS, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

**Depression**

Monitor females with a history of depression and discontinue NEXTSTELLIS if depression recurs to a serious degree. Data on the association of COCs with onset of depression or exacerbation of existing depression are limited.

**Cervical Cancer**

A causal relationship between the use of CHCs and the development of cervical cancer and intraepithelial neoplasia has not been clearly established. In observational studies, the use of oral hormonal contraceptives in females for five years or more, compared to females who did not use oral hormonal contraceptives, was associated with an increased risk of cervical cancer and intraepithelial neoplasia. In these studies, the use of oral hormonal contraceptives in females for 10 years or more, compared to females who received oral hormonal contraceptives for 5-9 years, was associated with an increased risk of cervical cancer and intraepithelial neoplasia. Limitations in these epidemiologic studies include potential recall bias, differences in sexual behavior, and other factors such as establishing whether there were data on persistent high-risk Human Papilloma Virus (HPV) infection.

**Hereditary Angioedema**

Avoid NEXTSTELLIS in females with hereditary angioedema. Exogenous estrogens may induce or exacerbate symptoms of hereditary angioedema.

**Chloasma**

Avoid NEXTSTELLIS in females with a history of chloasma gravidarum or increased sensitivity to sun and/or ultraviolet radiation exposure. Chloasma may occur with NEXTSTELLIS use, especially in females with a history of chloasma gravidarum.

### ADVERSE REACTIONS

The following clinically significant adverse reactions with the use of COCs are discussed elsewhere in labeling:

- **Serious cardiovascular events including venous and arterial thromboembolism** [See Boxed Warning and Warnings and Precautions]
- **Hyperkalemia** [see Warnings and Precautions]
- **Liver disease** [see Warnings and Precautions]

### Table 4 Adverse Reactions Occurring in ≥ 2% of Females Receiving NEXTSTELLIS in Studies C301 and C302

<table>
<thead>
<tr>
<th>Preferred Term (PT)</th>
<th>Participants with Adverse Reaction – US/Canada Phase 3 trial (n [%]) (N = 2073)*</th>
<th>Participants with Adverse Reaction – Two Phase 3 trials (n [%]) (N=3632)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse reaction</td>
<td>1205 (58.1)</td>
<td>2126 (58.5)</td>
</tr>
<tr>
<td>Mood disturbance</td>
<td>226 (10.9)</td>
<td>329 (9.1)</td>
</tr>
<tr>
<td>Bleeding irregularities</td>
<td>201 (9.7)</td>
<td>393 (10.8)</td>
</tr>
<tr>
<td>Breast symptoms</td>
<td>110 (5.3)</td>
<td>197 (5.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>100 (4.8)</td>
<td>227 (6.3)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>84 (4.1)</td>
<td>133 (3.7)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>68 (3.3)</td>
<td>108 (3.0)</td>
</tr>
<tr>
<td>Acne</td>
<td>66 (3.2)</td>
<td>136 (3.7)</td>
</tr>
<tr>
<td>Libido decreased/lost</td>
<td>27 (1.3)</td>
<td>72 (2.0)</td>
</tr>
</tbody>
</table>

*Represents the safety population of C302 only (US/Canada).

**Represents the safety population of C301/C302 for DRSP/E4.

1. Includes PTs: adjustment disorder, affective disorder, agitation, anger, anxiety, depressed mood, depression, depressive symptom, disorientation, emotional disorder, emotional distress, euphoric mood, generalized anxiety disorder, insomnia, irritability, mood altered, mood swings, nervousness, panic attack, panic disorder, performance fear, restlessness, sleep disorder, stress, suicidal ideation, tearfulness
2. Includes PTs: abnormal withdrawal bleeding, amenorrhea, cervic hemorrhoage uterine, coital bleeding, dysfunctional uterine bleeding, menometrorrhagia, menorrhagia, menstrual disorder, menstruation irregular, metrorrhagia, oligomenorrhea, polymenorrhea, uterine hemorrhage, vaginal hemorrhage.
3. Includes PTs: anisomastia, breast cyst, breast discolouration, breast discomfort, breast disorder, breast engorgement, breast enlargement, breast mass, breast edema, breast pain, breast swelling, breast tenderness, fibrocystic breast disease, galactorrhea, gynecomastia, mastoposis, nipple disorder, nipple pain.
4. Includes PTs: headache, premenstrual headache, and tension headache.
5. Includes PTs: adnexa uterine pain, dysmenorrhea, premenstrual cramps, pelvic discomfort, pelvic pain, uterine spasm.
6. Includes PTs: weight increased, weight fluctuation, body mass index increased, weight loss poor, and obesity.
7. Includes PTs: acne and cystic acne.
8. Includes PTs: libido decreased and loss of libido.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data provided reflect the experience with the use of NEXTSTELLIS in two large prospective studies, one in Europe/Russia (C301) and one in North America (C302) (N = 3,632) of NEXTSTELLIS for the prevention of pregnancy in females 16-50 years of age. The mean duration of NEXTSTELLIS exposure was 317 and 257 days for the respective studies. The study population was 27 years of age on average, with a mean BMI of 25 kg/m². The racial distribution was 83% White; 11% Black; 3% Asian; and 3% Other. Adverse Reactions Leading to Study Discontinuation (> 1%) Of 3,632 females in two clinical studies for prevention of pregnancy in females 16-50 years of age, 9.6% discontinued due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was bleeding irregularity (2.6%). Six subjects (0.17%) discontinued study participation due to new onset of migraine with aura; two subjects (0.05%) discontinued due to severe migraine. Thromboembolic Disorders and Other Vascular Problems During studies C301 and C302, one thromboembolic event was reported in a female who had been taking NEXTSTELLIS for 75 days and had normal BMI < 25 kg/m². Depression In Study C302 (US/CA), 36 (1.7%) subjects reported depression while using NEXTSTELLIS. Nine (0.3%) subjects had drug withdrawn as a result of symptoms of depression. Drug Interactions Effects of Other Drugs on Hormonal Contraceptives Clinically significant drug interactions with other drugs that affect NEXTSTELLIS are presented in Table 5. Effects of NEXTSTELLIS on Other Drugs Table 6 includes clinically significant drug interactions with NEXTSTELLIS that affect other drugs. Use in Specific Populations Pregnancy Risk Summary Discontinue NEXTSTELLIS if pregnancy occurs, because there is no reason to use hormonal contraceptives during pregnancy [see Contraindications]. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy. Reproductive toxicity studies performed with E4 alone have shown expected pharmacologic effects in animals, which are considered consistent with estrogen exposure. 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 Contraceptive hormones and/or metabolites are present in human milk. COCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing woman to use other methods of contraception until she discontinues breast-feeding [see also Dosage and Administration]. The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for NEXTSTELLIS and any potential adverse effects on the breast-fed child from NEXTSTELLIS or from the potential underlying maternal condition. After oral administration of /DRSP 3 mg/EE 30 μg, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum females within 24 hours. This results in a potential maximal daily dose of less than 1 μg DRSP in an infant.

Table 5. Clinically Significant Drug Interactions With Other Drugs that Affect NEXTSTELLIS

<table>
<thead>
<tr>
<th>CYP3A Inducers</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRSP is a CYP3A4 substrate. Concomitant use with strong CYP3A inducers or certain moderate or weak CYP3A inducers may decrease DRSP exposure [see Clinical Pharmacology], which may lead to contraceptive failure.</td>
<td></td>
</tr>
<tr>
<td>Prevention of Administration</td>
<td>Strong CYP3A Inducers</td>
<td>Avoid concomitant use. If concomitant use is unavoidable, use an alternative contraceptive method (e.g., intrauterine system) or backup non-hormonal contraceptive method during coadministration and up to 28 days after discontinuation of the strong CYP3A inducer.</td>
</tr>
<tr>
<td></td>
<td>Moderate and Weak CYP3A Inducers</td>
<td>Use an alternative or backup contraceptive method during coadministration and up to 28 days after discontinuation of the CYP3A inducer, unless the Prescribing Information of the specific moderate or weak CYP3A inducer indicates there is no clinically significant interaction with NEXTSTELLIS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP3A Inhibitors</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRSP is a CYP3A4 substrate. Concomitant use with a strong CYP3A inhibitor may increase DRSP exposure [see Clinical Pharmacology], which may increase the risk of adverse reactions of NEXTSTELLIS, including hyperglycemia [see Warnings and Precautions].</td>
<td></td>
</tr>
<tr>
<td>Prevention of Administration</td>
<td>Consider monitoring serum potassium concentration in patients who take a strong CYP3A4 inhibitor long-term and concomitantly with NEXTSTELLIS.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs that May Reduce the Absorption of NEXTSTELLIS</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concomitant use with drugs such as bile acid sequestrants may decrease the E4 and DRSP exposure, which may lead to contraceptive failure and/or an increase in breakthrough bleeding.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Separate time of administration of NEXTSTELLIS and the concomitant drug. Refer to the concomitant drug’s Prescribing Information for additional information.</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Clinically Significant Drug Interactions of NEXTSTELLIS on Other Drugs

<table>
<thead>
<tr>
<th>Anti-Diabetic Drugs</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NEXTSTELLIS may reduce the blood glucose lowering effect of anti-diabetic drugs [see Warnings and Precautions and Clinical Pharmacology].</td>
<td>Increase frequency of glucose monitoring and increase anti-diabetic drug dosage, as needed, based on glucose levels.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs that may increase serum potassium concentration</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a potential for an increase in serum potassium concentration in females taking NEXTSTELLIS with other drugs that may increase serum potassium concentration [see Warnings and Precautions and Clinical Pharmacology].</td>
<td>Monitor serum potassium concentration in females at increased risk for hyperkalemia.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lamotrigine</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NEXTSTELLIS may decrease lamotrigine exposure [see Clinical Pharmacology], which may reduce efficacy of lamotrigine.</td>
<td>Adjust lamotrigine dosage as recommended in its Prescribing Information based on NEXTSTELLIS initiation or discontinuation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Corticosteroids</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NEXTSTELLIS may increase the exposure of certain systemic corticosteroids, which may increase the risk of corticosteroid-related adverse reactions [see Clinical Pharmacology].</td>
<td>Follow the recommendation for the corticosteroid in accordance with its Prescribing Information. Consider more frequent monitoring for corticosteroid adverse reactions when used concomitantly with NEXTSTELLIS.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thyroid Hormone Replacement Therapy</th>
<th>Clinical Effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of NEXTSTELLIS may increase thyroid-binding globulin concentration [see Warnings and Precautions and Clinical Pharmacology].</td>
<td>Monitor thyroid-stimulating hormone (TSH) level and follow the recommendation for thyroid hormone replacement in accordance with its Prescribing Information.</td>
<td></td>
</tr>
</tbody>
</table>

Pediatric Use
Safety and efficacy of NEXTSTELLIS have been established in females of reproductive potential. The study population of C302 [see Clinical Studies] was in females of reproductive age 16-50 years of age. Use of NEXTSTELLIS before menarche is not indicated.

Geriatric Use
NEXTSTELLIS has not been studied in postmenopausal females and is not indicated in this population.

Hepatic Impairment
NEXTSTELLIS is contraindicated in females with hepatic impairment [see Contraindications, Warnings and Precautions]. The mean exposure to drospirenone (DRSP) in females with moderate liver impairment is approximately three times higher than the exposure in females with normal liver function. NEXTSTELLIS has not been studied in females with severe hepatic impairment [see Clinical Pharmacology].

Renal Impairment
NEXTSTELLIS is contraindicated in females with renal impairment [see Contraindications, Warnings and Precautions]. In subjects with creatinine clearance (CLcr) of 50–79 mL/min, serum DRSP levels were comparable to those in a control group with CLcr > 80 mL/min. In subjects with CLcr of 30–49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs [see Warnings and Precautions, Drug Interactions and Clinical Pharmacology].

Race/Ethnicity
No clinically significant difference was observed between the pharmacokinetics of E4 or DRSP depending on race [see Clinical Pharmacology].

Body Mass Index (BMI)/Body Weight
The safety and efficacy of NEXTSTELLIS in females with a BMI ≥ 35 kg/m² have not been adequately evaluated.

OVERDOSE
Overdosage of CHCs may cause nausea, vomiting, and severe headaches. Individual reports of thromboembolic complications and vaginal bleeding have occurred from overdosage. Pediatric patients with unintended CHC ingestion have reported nausea and vomiting and some developed irritability and drowsiness; rare reports described vaginal bleeding.

Overdosage Management
Consider short-term prophylactic anticoagulation therapy for patients with high risk of VTE. Monitor serum potassium and sodium levels, and for evidence of metabolic acidosis.
CLINICAL STUDIES
A total of 26 on-treatment pregnancies occurred in 1,524 females contributing 12,763 at-risk cycles. The overall Pearl Index was 2.65 (95% CI: 1.73-3.88) per 100 woman-years of use. Table 9 lists the Pearl Index by BMI subgroup. A trend of decreasing effectiveness with increasing BMI was observed in the study.

Table 9 Pearl Index Based on At-Risk Cycles and Reported Pregnancies in Females ≤ 35 Years of Age in Study C302

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N*</th>
<th>On-treatment pregnancies</th>
<th>At-risk cycles</th>
<th>Pearl Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study C302 BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>1,187</td>
<td>20</td>
<td>10,113</td>
<td>2.57 (1.57, 3.97)</td>
</tr>
<tr>
<td>≥ 30 to &lt; 35**</td>
<td>337</td>
<td>6</td>
<td>2,650</td>
<td>2.94 (1.08, 6.41)</td>
</tr>
</tbody>
</table>

* N = all females aged 16-35 with at least 1 at-risk cycle.
**One female with a BMI of 48 kg/m² was enrolled and included in the efficacy analysis.

Manufactured for:
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Greenville, NC.
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Results from a review of literature published in the journal *Cureus* indicate that patients with Type 2 diabetes (T2D) have increased susceptibility to oral and vulvovaginal candidiasis (VVC). Lead author Lubna Mohammed, MBBS, Internal Medicine at the California Institute of Behavioral Neurosciences & Psychology, and her colleagues conducted a review of articles published between 2000 and 2021. Investigators searched PubMed for studies that analyzed the relationship between candidiasis prevalence and T2D. They also examined the pathogenesis of *Candida* species and why they affect patients with T2D. The authors searched PubMed for studies that analyzed the relationship between candidiasis prevalence and T2D. They also examined the pathogenesis of *Candida* species and why they affect patients with T2D.

Search terms investigators used included: diabetes mellitus, *Candida*, candidiasis, oral candidiasis, vulvovaginal candidiasis, candidiasis and diabetes mellitus, oral candidiasis in diabetics, and vulvovaginal candidiasis in diabetics. Investigators reported no demographic restrictions were used during the review process. Incomplete articles, publications without abstracts, and articles published before the year 2000 were excluded. Investigators did not use age or ethnicity as defining factors in the search.

While *Candida* is normally found in the oral cavity, investigators noted that *Candida* flourishes in patients with T2D due to elevated glucose levels, which can result in oral candidiasis and dental plaques. *Candida* is normally found in the oral cavity, investigators noted that *Candida* flourishes in patients with T2D due to elevated glucose levels, which can result in oral candidiasis and dental plaques. "Out-of-control blood glucose levels result in various metabolic changes, like a rise in glycogen levels. This can cause a remarkable increase in the colonizing and pathogenic abilities of *Candida* species, as raised glycogen levels cause a fall in the pH of the vagina, making the environment more susceptible to the establishment of a VVC community," the authors wrote. They also noted that patients may have asymptomatic infection due to the immune system keeping the infection contained.

The authors said T2D affects millions of patients globally and makes this population more susceptible to secondary infection due to weakened immunity and blood glucose levels that are uncontrolled. In the study, they noted that "one such frequently prevalent infection is candidiasis, due to pathogenicity by *Candida* species due to candidalysin, (serum amyloid P component) proteins, and biofilm production." They explained that biofilm makes treatment challenging because it is resistant to antifungal medications. Based on the results of the literature review, investigators concluded that oral candidiasis is widespread in patients with T2D, and that these patients are at higher risk for these infections than healthy people. Investigators reported the same results for VVC: Patients with T2D are at higher risk than healthy individuals.

In an interview with *Contemporary OB/GYN®,* Mohammed said the most significant finding of this study for practicing providers is to watch for symptoms of VVC in women with T2D.

Symptoms of VVC include white, cottage cheese-like discharge, edema, redness, pain, and burning sensation. Investigators noted occasional evantuating dysuria and dyspareunia. "Out-of-control blood glucose levels result in various metabolic changes, like a rise in glycogen levels. This can cause a remarkable increase in the colonizing and pathogenic abilities of *Candida* species, as raised glycogen levels cause a fall in the pH of the vagina, making the environment more susceptible to the establishment of a VVC community," the authors wrote. They also noted that patients may have asymptomatic infection due to the immune system keeping the infection contained.

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In an interview with *Contemporary OB/GYN®,* Mohammed said the most significant finding of this study for practicing providers is to watch for symptoms of VVC in women with T2D.
preferences of the patient. Diagnostic certainty, and thus advice about delivery management, is improved if there are elevated transaminases or a history of ICP in prior pregnancies, and it may be reasonable to deliver in the absence of bile acid results in these situations. We recommend against preterm delivery at <37 weeks of gestation in patients with a clinical diagnosis of ICP without laboratory confirmation of elevated bile acids (GRADE 1B). On disease outcomes.” She added that larger study population groups should be examined. “The isolation of Candida strains from people with T2D and comparing their counts in healthy subjects is also needed,” she said.

The study’s limitations, according to Mohammed were due to the small number of articles published that focused on the direct relationship between candidiasis and T2D. In addition, she noted that “several strains of Candida exist, and the studies included in this article do not differentiate amongst which strain is predisposing to more significant susceptibility infections in [participants with T2D]. Ob/gyn providers and researchers can consider studying these points in detail.”

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

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Society for Maternal-Fetal Medicine Consult Series #53

CONTINUED FROM PAGE 13

What is the likelihood of recurrence?
The risk of recurrence of ICP in subsequent pregnancies may be as high as 90%, although data are insufficient to counsel patients on specific ranges. Some data also suggest that patients with a history of ICP are at higher risk for developing later hepatobiliary disease, particularly within the first year after the diagnosis of ICP. Given the risk for hepatitis C in these patients and the availability of an effective treatment, some experts advocate for routine testing for hepatitis C in patients with ICP. It is important to consider reevaluation of liver function test results after delivery in patients with persistent pruritis or other signs or symptoms of a hepatobiliary disease, such as right upper quadrant pain or jaundice. If serologic study results remain abnormal, the patient should be referred to a liver specialist for evaluation for another underlying condition.

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Genetic Factors for Reproductive Aging and Vasomotor Symptoms

by BOB KRONEMYER

Genetic factors predictive of reproductive aging are also linked to vasomotor symptoms (VMS), indicating a polygenic architecture for VMS, according to an analysis of the Study of Women’s Health Across the Nation (SWAN) Genomic Substudy.

The analysis of a multiracial/ethnic cohort in the journal *Menopause* found that in White women only, there was an association between the protein-coding gene *TACR3* and VMS. But among Chinese and Japanese women, all 14 *TACR3* single-nucleotide polymorphisms (SNPs) were monomorphic or extremely rare.

“Most women experience some VMS as they transition through menopause,” said principal investigator Sioban Harlow, PhD, a professor of epidemiology and global public health at the University of Michigan in Ann Arbor. “And a subset of women experience severe and bothersome hot flashes that last, on average, more than 5 years.”

The investigators created polygenic risk scores (PRSs) from genome-wide association studies of VMS and ages at menarche and menopause for 702 White, 306 Black, 126 Chinese, and 129 Japanese women.

Since enrollment in SWAN across 7 sites in 1996 and 1997, participants have had, on average, 15 follow-up visits. The study investigators also remain in contact with 75% of surviving participants.

At each visit, women completed an interviewer-administered and self-administered questionnaire on a broad range of topics, including menstrual characteristics, current use of hormone therapy (HT) for menopausal symptoms, and symptom experience.

Increasing scientific understanding of the biological pathways that underlie hot flashes is critical.

“Genetic factors associated with age at menopause and age at menarche were associated with VMS in some but not all race/ethnic groups, suggesting that VMS has a polygenic architecture,” Harlow told *Contemporary OB/GYN*. “Specifically, in Black women, a higher PRS for older age at menarche was associated with a 45% reduction in the odds of frequent VMS (≥6 days in the past 2 weeks at any visit) and of experiencing a sustained high-frequency VMS trajectory.”

But in White women, a higher PRS for older age at menarche was connected to only a 25% reduction in the odds of having a frequent VMS trajectory with onset at final menstrual period.

“Chinese women with a higher PRS for older age at menopause had a 2-fold increase in the odds of having frequent VMS,” Harlow said.

The authors expected to replicate findings of a link between VMS and *TACR3*. “However, findings of associations with PRSs for age at menopause and age at menarche are novel,” Harlow said.

The proportion of women who ever used HT during follow-up ranged from 33.3% for Chinese women to 52.7% for White women, with 6.1% to 25% reporting HT use at any given visit.

A total of 70.7% of White, 79.4% of Black, 51.6% of Chinese, and 52.7% of Japanese women ever reported frequent VMS.

“Increasing scientific understanding of the different biological pathways that underlie hot flashes is critical for innovation in the prevention and treatment of bothersome vasomotor symptoms,” said Harlow, director of the Center for Midlife Science at the University of Michigan. “Validation of the causal effects of specific SNPs in vitro could also provide support for new targets for VMS alleviation, such as the use of neurokinin B pathway agents. Replication in larger samples in diverse populations is needed as well.”

DISCLOSURES Harlow reports no relevant financial disclosures.

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

FOR REFERENCES VISIT contemporaryobgyn.net/VMS
The sexually transmitted, pathogenic bacterium *Mycoplasma genitalium* (*M. genitalium*) is difficult to diagnose, challenging to treat, and poorly understood, despite its growing prevalence among sexually transmitted infections. How should clinicians approach testing and therapy?

In this *Contemporary OB/GYN*® podcast, Amesh Adalja, MD, discusses current data on *M. genitalium*, including its frequent presence as a coinfection; diagnosis strategies and newly available nucleic acid amplification testing; and the bacterium’s antibiotic resistance that underlines the importance of HCP education and awareness.

**Listen to the podcast:**
contemporaryobgyn.net/m-genitalium-considerations
New Mother’s Thumb

by JONATHAN E. ISAACS, MD

A 28-year-old woman presents 3 months postpartum complaining of left wrist pain. She localizes the pain to the radial aspect of her left nondominant wrist and reports radiation into the thumb. Nonsteroidal antiinflammatory drugs (NSAIDs) provide limited relief and the pain is exacerbated with lifting or breastfeeding. The pain started in her third trimester of pregnancy and has gradually worsened.

What’s Going On?
De Quervain tenosynovitis—actually a misnomer since the condition lacks any true inflammatory component—is the clinical manifestation of stenotic changes to the tendon sheath surrounding the abductor pollicis longus and extensor pollicis brevis tendons as they pass over the radial styloid toward their insertion points at the base of the thumb metacarpal and the proximal phalanx, respectively. Believed to be induced by increased pressure or friction between the tendons and the inner tendon sheath, the sheath

Isaacs is a professor and the chief of hand surgery in the Department of Orthopaedic Surgery at the Virginia Commonwealth University Health System in Richmond.
undergoes myxoid degeneration and can become grossly thickened (up to 5 times the normal sheath wall thickness).1

The monikers “new mother’s thumb” or “mother’s wrist” stem from the increased incidence of this disorder seen during the third trimester of pregnancy and in the first few months after delivery, especially if breastfeeding.2 Repetitive lifting and the extreme wrist positioning necessary to support the newborn baby’s head during breastfeeding subject the affected tendon sheath to abnormal stresses, which certainly could explain the pathologic changes. Fluid retention and even a hormonal component (possibly related to prolactin)2-4 have been proposed as additional etiologies and offer a more likely mechanism for women who develop antepartum symptoms.

**Presentation**

Pain localized over the radial styloid with
Figure 3. Brunelli test. The patient extends their thumb (as if hitchhiking) and tries to maintain the thumb in this position as the examiner pushes the thumb down. Pain radiating either into the thumb or proximally along the tendon sheath would be indicative of De Quervain tenosynovitis.

Figure 4. The appropriate splint will immobilize the thumb.

radiation both proximally and distally into the thumb is the most common presentation. Patients will sometimes report stiffness or a catching sensation coming from the radial side of the wrist. Paresthesia affecting the dorsal proximal thumb skin is an occasional complaint, most likely due to irritation of the nearby superficial branch of the radial nerve; this should not be confused with sensory disturbances confined to the fingertips, which is more indicative of gestational carpal tunnel syndrome.

Patients often will have focal swelling (Figure 1) and point tenderness on the radial aspect of the wrist. Pain associated with provocative maneuvers supports the diagnosis by either stretching the involved tendons or straining the tendons against the tendon sheath.

- **FINKELESTEIN TEST:** With the wrist positioned thumb toward the ceiling, the examiner grasps the affected thumb and pulls it down and toward the floor.\(^5\)

- **EICHHOFF MANEUVER:** Same starting position, but the patient grasps their thumb with the fingers of the affected hand and ulnarly deviates the wrist toward the floor (Figure 2).\(^6\)

- **BRUNELLI TEST:** Patient holds the thumb up like they are hitchhiking against resistance applied by the examiner (Figure 3).\(^7\)

### Initial management by an obstetrician

Many of these patients will respond to conservative treatment including NSAIDs, temporary thumb spica splint immobilization (Figure 4), and ice application. Topical antiinflammatory agents can be effective as well. A common mistake is to apply a wrist splint, which does not immobilize the thumb and can actually exacerbate the condition as the thumb struggles to work around the splint! Often, symptoms will spontaneously resolve within a few months of delivery or after the patient discontinues breastfeeding. Patients with persistent symptoms (especially if significant swelling is noted) will benefit from referral to a hand surgeon for additional treatment options. These can include steroid injections or, in some cases, surgical release—both of which have high rates of success.\(^8\)

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Should Suspicion of Maternal/fetal Infection Have Led to Earlier Delivery?

Factual Summary
The patient transferred her care to defendant hospital on June 3, 2011, when she was 36 weeks and 6 days pregnant. Nonparty ob/gyn followed her for her prenatal care through May 2011. During this time, the pregnancy had progressed normally, with the exception of gestational diabetes, which was controlled by diet. Other than the known gestational diabetes, the patient’s pregnancy continued to progress normally under the care of Defendant ob/gyn with weekly prenatal visits and fetal nonstress tests, all of which were reactive. Following her final prenatal visit on July 1, she was scheduled for induction of labor on July 5, 2011.

On July 3, 2011, the patient presented to the labor-and-delivery department at defendant hospital accompanied by her husband. She reported painful contractions since 10 AM, now occurring 2 minutes apart. Her vitals at the time of triage included a temperature of 96.1 F, heart rate of 90 beats per minute (BPM), and blood pressure of 131/69. She denied leaking of fluid or vaginal bleeding and reported active fetal movement. Her last group strep B (GBS) test on May 26 was negative; she was not in distress, her membranes were intact, she was 3 to 4 cm dilated, 50% effaced, and was at –3 station. Defendant ob/gyn was present for the cervical exam. External fetal monitoring was established and the infant’s baseline heart rate was 145 BPM with moderate variability, spontaneous accelerations, and no decelerations. The patient was admitted for a nonurgent delivery and the resident ordered continuous external fetal monitoring, routine labs, penicillin for unknown GBS, and an intravenous line (IV) for fluids. Defendant ob/gyn’s first note was written at 5:28 PM, wherein he reiterated much of the resident’s findings and determined that prophylaxis for GBS was not necessary since the mother had no risk factors. The first documented deceleration occurred at 6:15 PM. At that time, the fetal heart rate (FHR) decreased from 145 to 60 BPM for 10 seconds and recovered. The fetal heart tracing was considered a category 1. The patient requested a spinal epidural, which was started shortly after 6:30 PM. Defendant ob/gyn noted intermittent variable decelerations on the fetal monitoring at 9:13 PM. The patient was turned to her left side, oxygen was administered via a nonrebreather mask, and the FHR returned to 140 BPM with moderate variability. Defendant ob/gyn indicated that “overall,” the FHR was reassuring.

The FHR was 155 BPM, with moderate long-term variability, and no decelerations. Cervical exam showed 2 to 3 cm dilated, 80% effaced, and –3 station. Her membranes were ruptured manually and meconium was noted. Defendant ob/gyn documented that the patient was in early labor and the FHR was reassuring, so labor was allowed to continue. At 8 PM, a second deceleration occurred following a contraction. The FHR decreased from 145 to 60 BPM for 100 seconds and made a variable, spontaneous recovery. The tracing was considered a category 2 and the nursing staff turned the patient on her left side. A nursing shift-change note at 9:01 PM noted a third deceleration where the FHR decreased from 145 to 80 BPM for 120 seconds following a contraction. The patient remained on her left side and the rate of the IV fluids was increased.

Defendant ob/gyn noted intermittent variable decelerations on the fetal monitoring at 9:13 PM. The patient was turned to her left side, oxygen was administered via a nonrebreathe mask, and the FHR returned to 140 BPM with moderate variability. Defendant ob/gyn indicated that “overall,” the FHR was reassuring.

Andrew I Kaplan, JD, is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation. This case was handled by one of his partners.
However, at 9:41 pm, Defendant ob/gyn was called to the patient’s room for a deceleration to 60 BPM for 4 minutes. The patient was placed on all fours, which caused the loss of external monitoring, so Defendant ob/gyn placed an ion-sensitive electrode and the patient was repositioned to her left side. Defendant ob/gyn reported spontaneous resolution of the decelerations and baseline FHR “now” 155 BPM, with moderate variability. He discussed with the patient and her husband that she still was in latent labor, so immediate intervention was not necessary; however, the possibility of a cesarean delivery was discussed. He noted that prior to this deceleration several intermittent variable decelerations had occurred, so they would follow the fetal monitoring closely. At 9:54 pm, the patient’s temperature was 98.4 F, her heart rate was 87 BPM, and her blood pressure was 131/72. At 10:16 pm, Defendant ob/gyn ordered oxytocin injection (Pitocin); however, this was never administered. On exam, the patient was 3 cm dilated, 80% effaced, and -2 station. The record indicates that she had a “spontaneous” rupture of membranes, which were meconium stained, and she was having 1 to 5 contractions every 10 minutes. The FHR was 110 to 160 BPM, with moderate variability with accelerations and intermittent variable decelerations. At 11:30 pm, a second prolonged deceleration was noted when the FHR decreased to 55 BPM for 3 minutes and 20 seconds. The patient was placed on her left side and then on her hands and knees, oxygen was given by mask, and IV fluids were opened wide. A third prolonged deceleration was noted at 12:45 AM on July 4. The FHR decreased from 130 to 65 BPM for 5 minutes with a gradual recovery. Again, the patient was placed on her left side and then on her hands and knees, oxygen was given by mask, and IV fluids were opened wide. Defendant ob/gyn was notified.

Initially the infant had limp muscle tone and was blue/pale in color.

On July 4, at 1:24 AM, Defendant ob/gyn noted that there had been several decelerations lasting 2 to 4 minutes over the course of the evening, with the most recent decelerations at 11:30 PM and 12:45 AM. He discussed with the patient and her husband the possibility of an emergent C-section if the FHR did not recover following a deceleration. At 4:02 AM, an OB resident noted that the patient was in latent labor and the FHR was in the 140s with moderate variability, no accelerations, and 3 variable decelerations to the 130s in the past 10 minutes. Her tracing was still a category 2. At 4:30 AM, the FHR decelerated from 150 to 115 BPM for 40 seconds with a variable recovery. Fifteen minutes later, another deceleration from 150 to 70 BPM for 140 seconds was observed. Later, at 5:30 AM, the FHR decelerated from 155 to 130 BPM for 2 minutes with a gradual recovery. The variability was minimal, no accelerations were noted, and the tracing remained a category 2.

At 6:55 AM, Defendant ob/gyn indicated that there had been no change in the patient’s condition since the last exam, and he recommended a C-section. The patient’s heart rate was 105 BPM at 7:00 AM and continued in the range of 100 to 113 BPM between 7:45 AM until she was taken to the operating room (OR) at 8:40 AM. She never became febrile, as her highest temperature reading was 99.6 F at 7:45 AM. During the roughly 2 hours between the call for a C-section and the patient being taken to the OR at 8:40 AM, the fetal monitoring strips were interpreted by the nurses as showing a baseline heart rate of between 150 and 155 BPM until 7:45 AM, and then between 160 to 165 BPM with moderate variability; 5 decelerations were noted at 7:15, 7:30, 7:45, 8:00, and 8:15 AM.

According to the intraoperative nursing note, the patient was in the OR at 8:40 AM and the incision was made at 8:54 AM. A female infant was delivered at about 9:20 AM. Defendant ob/gyn reported thick meconium upon entering the uterus. The infant was delivered and handed off to the waiting pediatricians. The placenta was sent to pathology. The pathology report dated July 7 indicated that the placenta was mature and that there were fetal membranes with meconium-filled macrophages. Further, pathology confirmed acute chorioamnionitis involving the extraplacental membranes, chorionic plate, and chorionic plate vessels, as well as severe, acute funisitis involving umbilical vessels and extending into Wharton jelly. Finally, pathology noted meconium-filled macrophages in the umbilical cord. Initially, the infant had limp muscle tone and was blue/pale in color. However, 10 minutes after birth, she had a strong cry, flexed her extremities, and was completely pink. The infant was 51 cm long and weighed 3.575 kg at the time of delivery. Upon delivery, it was report-
ed that she cried for 30 seconds, but was then apneic for 2 minutes. She was bagged and masked for positive pressure ventilation (PPV) from about 2.5 minutes to 6 minutes. Her heart rate was above 60 BPM but dipped from the 100s to the 60s when she became apneic. Her oxygen saturation (SpO₂) levels were in the 70s and did not increase with PPV, so she was placed on continuous positive airway pressure (CPAP) with 40% oxygen followed by 60% oxygen when her SpO₂ remained at 88%, with increased saturations to the high 80s/low 90s by 10 minutes. She began breathing independently around 8 minutes and was continued on CPAP.

The infant's APGAR scores were 4, 5, and 9 at 1, 5, and 10 minutes after delivery. Her initial venous cord gases, taken at 9:09 AM, were pH 7.15, BE –11.1, pCO₂ 51, PO₂ 85. Initial white blood cell count was 15.3. She was transported to the neonatal intensive care unit (NICU) on CPAP. The infant was admitted to the NICU. Neonatology’s initial impression included a term female with hypoxic respiratory failure likely secondary to pulmonary arterial hypertension, presumed sepsis/pneumonia, and relative hypotension. She was responsive to tactile stimulation and had a regular heartbeat, but had diminished breath sounds, a weak cry, weak grasp, and weak rooting and sucking. CPAP was increased to 100% due to increased oxygen requirements and, eventually, the infant required intubation along with hand-bagging to correct hypoxemia. Blood cultures were taken and she was started on ampicillin and gentamicin. The next day, the infant was removed from the oscillator and placed on conventional ventilator support per neonatology’s order. Initial blood cultures (stain) confirmed gram-negative rods, and antibiotics were continued. She remained sedated on midazolam (Versed) and morphine. During the afternoon of July 6, she began to deteriorate. During the evening of July 6, neonatology ordered that she be placed on extracorporeal membrane oxygenation (ECMO) and she was cannulated at bedside without difficulty. Blood cultures confirmed pan-sensitive Escherichia coli and antibiotics were continued for Escherichia coli meningitis. Blood cultures taken on July 7 grew out multidrug resistant (MDR) Klebsiella pneumoniae on July 9, both peripherally and from the ECMO circuit. Her antibiotic regime was then changed from cefotaxime to meropenem and tobramycin. Over the next 4 days, the infant continued to have respiratory distress with desaturations into the mid- to low- 80s, hypotension, thrombocytopenia, leukopenia, neutropenia, E coli sepsis, pneumonia, MDR K pneumoniae septic shock, and persistent pulmonary hypertension, in addition to worsening renal failure, anemia, persistent metabolic acidosis, high blood lactate, and anuria. Her prognosis remained poor and, on July 11 at 7:45 AM, the father elected to withdraw ECMO support and continuous venovenous hemodialysis. She died 5 minutes after support was withdrawn.

Mom’s urine cultures returned with gentamycin-resistant K pneumoniae, which, per the note, was the same as found in the infant; cefepime was started after consultation with the infectious disease department. The patient’s lochia culture revealed many Pseudomonas aeruginosa and few K pneumoniae; the blood culture was negative; and the urine culture showed >100,000 colony-forming units/mL K pneumoniae. On this date, the patient also requested a psychiatric consult.

Plaintiff provided a medical consultation report for an exam of the patient performed on September 28, 2016. The patient presented with dyspareunia. She reported that this has existed since “the ‘traumatic’ (complicated) delivery in 2011.” The report further indicated that she had used medication, including oxycode, paracetamol, and ibuprofen, postoperatively since the delivery in 2011, and that she had remained on medication, including tramadol and oxycode, which she uses 1 hour before any sexual intercourse and during her ovulation, which occurs 4 days per month. She also complained of menorrhagia and dysmenorrhea.

**Allegations**

The plaintiffs alleged that the fetal monitoring strips showed signs of fetal distress on a number of occasions throughout the labor that warranted earlier delivery by C-section. They also claimed that as a result of the misinterpretation of the strips and/or the failure to appreciate signs of distress on the strips, Defendant ob/gyn and hospital failed to timely diagnose and properly treat the arrest
of labor. Further, they alleged that Defendant ob/gyn and hospital failed to appreciate signs of infection 2 hours before the delivery and, thus, caused a further delay of about 2 hours between the call for delivery and the actual delivery. Plaintiffs claimed that thereafter, the patient was untimely and improperly treated for the infection, causing her infection to be more severe. The injuries claimed to be suffered by the infant include pain and suffering, infection, mental anguish, emotional distress, anxiety, fear of dying, and death due to an HAI. The alleged injuries suffered by the patient included pain and suffering, infection, infected surgical wound, administration of antibiotics, having to seek additional medical care, having to undergo extensive tests, being incapacitated from attending to her usual duties, painful sexual intercourse, menorrhagia, and dysmenorrhea. The mother’s emotional damages for the infant’s death were dismissed pursuant to the decision on our motion for summary judgment.

**Discovery**

The patient testified that she experienced no fevers, sweating, tachycardia, or other signs of an infection in the weeks and days leading up to her labor or during her labor. She and her husband both testified to Defendant ob/gyn’s presence throughout the labor. They also claimed that the neonatologist told them that he felt, because of the strong and prolonged decelerations, that the C-section should have been performed earlier; according to the plaintiffs, the neonatologist said that the delay in the performance of the C-section was malpractice and that he felt the infant’s outcome would have been different if the C-section had been performed earlier.

Defendant ob/gyn confirmed that the plaintiff was delivered by C-section because of failure to progress relating to an arrest in dilation. He advised that it is possible for an infection to be asymptomatic, which this one was, and that no sign or symptom suggested an infection during labor. He stated that chorioamnionitis is not an indication for surgery, nor is meconium. The presence of meconium did not change his management of the labor. He advised that an increase in the maternal or fetal heart rate alone or together does not diagnose chorioamnionitis, but that maternal fever and fetal tachycardia together would raise the suspicion of chorioamnionitis. Defendant ob/gyn confirmed that a maternal temperature of 99.6 F was not a fever, and the mother’s temperature never rose above this until after the delivery in the recovery room. In regard to the fetal monitoring strips, he testified that overall the baseline heart rate ranged from 140 to 155 BPM; the strips were reactive with moderate variability and thus were reassuring. He confirmed that he was aware of the multiple prolonged decelerations, but that there was never any point in time that the strips suggested an urgent or emergent reason to deliver the infant. He would read the strips in long segments rather than section by section and, therefore, he was looking at the big picture of the labor. Defendant ob/gyn testified that, as standard, obstetricians attempt to do a C-section within 30 minutes of the call for it; extending the labor unnecessarily risks bleeding for the mother and infection for both mother and baby. He confirmed that this was not an urgent or emergent delivery, and when confronted with the fact that this plaintiff was not in the OR until 8:40 AM, almost 2 hours after the decision for the C-section was made, he testified that the delay could have been caused by the ORs being occupied. The neonatologist confirmed that the baby had bacteremia at the time of birth and that this later became sepsis. He felt there was no reason to suspect an MDR K pneumoniae and that this is what ultimately caused the infant’s death.

Based upon the fact that the strips were not consistently reactive and did, in hindsight, suggest that the baby was sick, we estimated that the likelihood of a defense verdict was essentially a 50/50 proposition. We would have to walk a fine line in presenting a defense that suggested the infection was present prior to plaintiff’s hospital presentation but was not detectable or diagnosable prior to the delivery of the child, as the infection presented with no symptoms. This argument would place Defendant ob/gyn in a precarious position, as he was the physician in charge of the patient’s prenatal care, as well as her 17-hour labor at the hospital. Nonetheless, given the plaintiff’s 7-figure demand and the support of our experts in ob/gyn and infectious diseases, the decision was made to proceed to trial. In the process of trial preparation and the scheduling of witnesses, the patient’s attorney proposed further negotiations and the case ultimately settled as to the hospital, only, for a more reasonable 6-figure award.
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Olive View-UCLA Medical Center, a Los Angeles County facility and major teaching hospital for the David Geffen School of Medicine at UCLA, is recruiting a full-time BC/BE general obstetrician/gynecologist.

We are seeking individuals who will contribute to an academic, energetic and creative multidisciplinary faculty. Responsibilities include direct patient care with strong emphasis on mentoring and training residents in the UCLA Ob/Gyn Residency Program, as well as the teaching of medical students. Opportunities in clinical and health services research are available and encouraged. Employment includes an academic appointment at the David Geffen School of Medicine at UCLA. Competitive salary and benefits provided. We are committed to excellence and equity in every facet of our mission. We welcome candidates whose experience in teaching, research, or community service has prepared them to contribute to our commitment to diversity and excellence. Applicant must be eligible for licensure in California. EOE

*Please submit letter of intent, CV, and three references to:*
Dr. Christine Holschneider, Chair, Department of Obstetrics and Gynecology, Olive View-UCLA Medical Center, Sylmar, CA 91342; via email: cholschneider@dhs.lacounty.gov
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