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OBG MANAGEMENT

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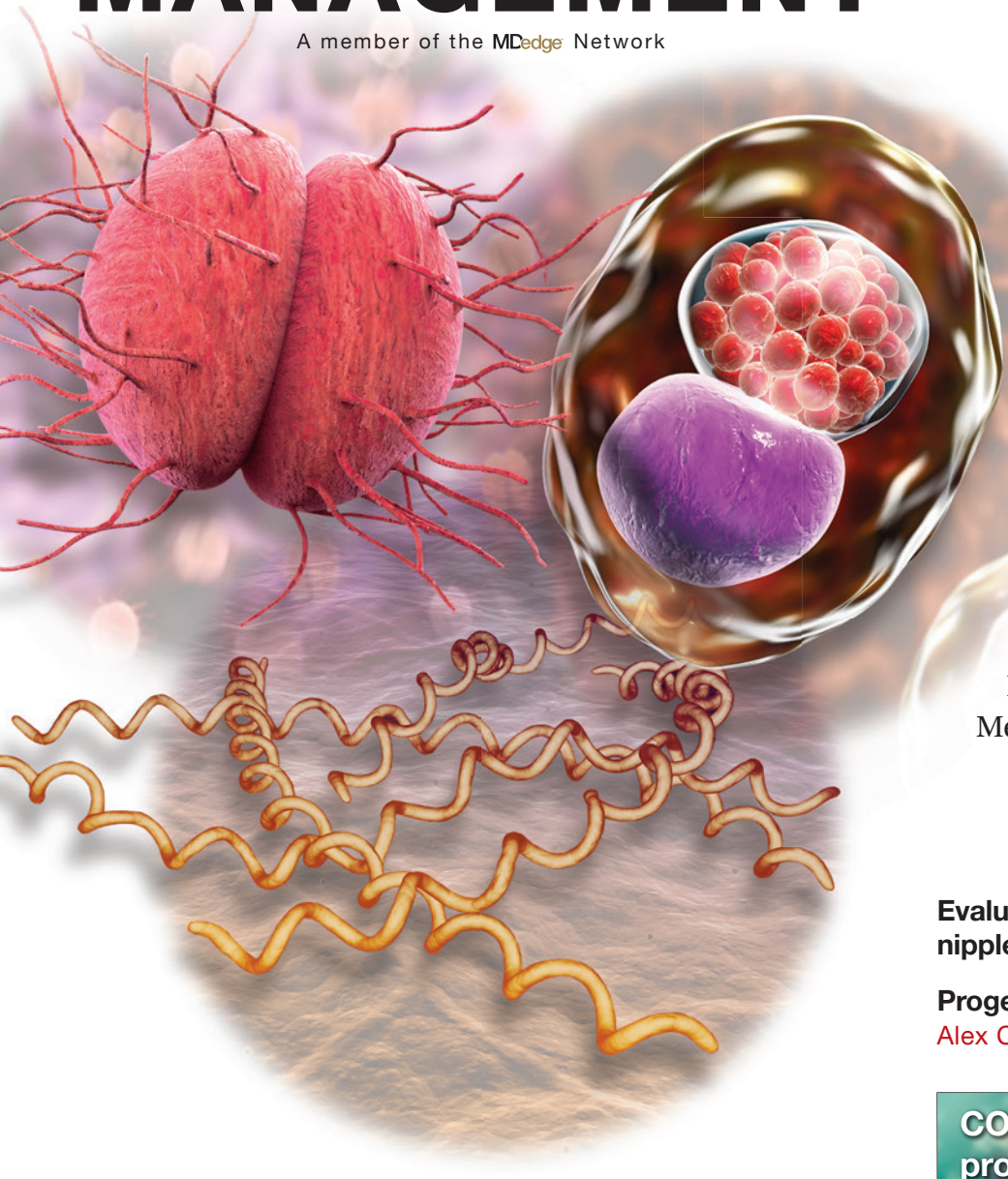

The STD epidemic

Why we need to care

Lisa B. Haddad, MD, MS, MPH;
Melissa J. Kottke, MD, MPH, MBA

~44 million patients remain unscreened for colorectal cancer (CRC).[1-7]*
Some of them may even be in your practice.

TAKE ON SUBOPTIMAL SCREENING RATES

ONE YES AT A TIME

Cologuard® is intended to screen adults aged 45 years and older at average risk for CRC.

In a prospective, head-to-head, point-in-time, 90-site, pivotal study of 10,000 patients aged 50-84 years at average risk for CRC, published in *The New England Journal of Medicine*, Cologuard demonstrated[8†]:

92%
SENSITIVITY OVERALL
In detecting CRC stages I to IV[8‡]

94%
SENSITIVITY IN EARLY CRC
In detecting CRC stages I to II[8,9‡]

87%
SPECIFICITY OVERALL
In patients with nonadvanced adenomas, nonneoplastic findings, or negative colonoscopy results[8§]

99.94%
NEGATIVE PREDICTIVE VALUE
If a patient received a negative test result, there was a 99.94% chance that there was no CRC[8||]

Indication and Important Risk Information

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 45 years or older, who are at typical average risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Cologuard is not for high-risk individuals, including patients with a personal history of colorectal cancer and adenomas; have had a positive result from another colorectal cancer screening method within the last 6 months; have been diagnosed with a condition associated with high risk for colorectal cancer such as IBD, chronic ulcerative colitis, Crohn's disease; or have a family history of colorectal cancer, or certain hereditary syndromes.

Positive Cologuard results should be referred to diagnostic colonoscopy. A negative Cologuard test result does not guarantee absence of cancer or advanced adenoma. Following a negative result, patients should continue participating in a screening program at an interval and with a method appropriate for the individual patient.

False positives and false negatives do occur. In a clinical study, 13% of patients without colorectal cancer or advanced adenomas received a positive result (false positive) and 8% of patients with cancer received a negative result (false negative). The clinical validation study was conducted in patients 50 years of age and older. Cologuard performance in patients ages 45 to 49 years was estimated by sub-group analysis of near-age groups.

Cologuard performance when used for repeat testing has not been evaluated or established. Rx only.

Offer Cologuard to your average-risk patients as a CRC screening option from the start.

Visit cologuardhcp.com

*Estimate based on the US population aged 45 to 74 years as of 2018, adjusted for the reported rates of high-risk conditions and prior screening history for CRC.
†In the pivotal study, screening colonoscopy was the reference method.[8]
‡Cologuard sensitivity, per stage of cancer: I: 90% (n=29); II: 100% (n=21); III: 90% (n=10); IV: 75% (n=4).[8]
§Cologuard specificity: 87% overall specificity, excluding CRC and advanced adenomas, and including all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy. There was 90% specificity in participants with no lesions biopsied on colonoscopy.[8]
‖Negative predictive value (NPV) is defined as the probability that disease is absent in those with a negative result; it is highly dependent on the prevalence of the disease. NPV was derived from the patient population evaluated in the Imperiale et al publication.[8]

References: 1. Annual estimates of the resident population for selected age groups by sex for the United States: April 1, 2010 to July 1, 2018. United States Census Bureau website. https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2018_PEPAGESEX&prodType=table. Updated June 2019. Accessed January 9, 2020. **2.** SEER cancer statistics review 1975-2016. Howlader N, Noone AM, Krapcho M, et al, eds. National Cancer Institute website. https://seer.cancer.gov/csr/1975_2016/browse_csr.php?sectionSEL=6&pageSEL=sect_06_table.10. Updated September 5, 2019. Accessed January 9, 2020. **3.** Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. *Genet Med*. 2015;17(9):702-712. **4.** Loftus EV Jr. Update on the incidence and prevalence of inflammatory bowel disease in the United States. *Gastroenterol Hepatol (NY)*. 2016;12(11):704-707. **5.** *Colorectal Cancer Facts & Figures 2017-2019*. American Cancer Society website. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2017-2019.pdf. Accessed January 9, 2020. **6.** Fedewa SA, Siegel RL, Jemal A. Are temporal trends in colonoscopy among young adults concordant with colorectal cancer incidence? *J Med Screen*. 2019;26(4):179-185. **7.** Use of colorectal cancer screening tests: 2018 Behavioral Risk Factor Surveillance System. Centers for Disease Control and Prevention website. https://www.cdc.gov/cancer/colorectal/statistics/use-screening-tests-BRFSS.htm. Updated October 22, 2019. Accessed January 9, 2020. **8.** Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014;370(14):1287-1297. **9.** Ahlquist DA. Multi-target stool DNA test: a new high bar for noninvasive screening. *Dig Dis Sci*. 2015;60(3):623-633.

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*Source: Kantar Media, Medical Surgical Study December 2019, Obstetrics/Gynecology Combined Office & Hospital Readers.
†OBG MANAGEMENT recognizes the importance of addressing the reproductive health of gender-diverse individuals.

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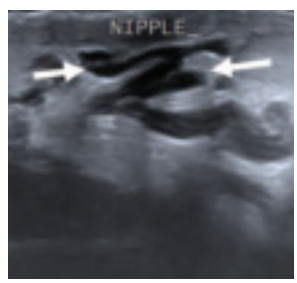

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Only **Paragard® (intrauterine copper contraceptive) IUS**, with 1 hormone-free active ingredient (copper), delivers the **strongest combination of benefits for the widest range of women**[1,2*]

The Paragard Promise:

- Proven >99% efficacy
- 100% hormone free
- Pregnancy prevention for up to 10 years
- Immediately reversible whenever she decides

Satisfy more patients with Paragard—the only highly effective, reversible birth control that is completely hormone free. Learn more at **hcp.paragard.com** or call **1-877-PARAGARD**.

Indication

Paragard is a copper-containing IUS (intrauterine system) indicated for the prevention of pregnancy for up to 10 years.

Important Safety Information

- Paragard must not be used by women who had a post-pregnancy or post-abortion uterine infection in the past 3 months; have cancer of the uterus or cervix; acute pelvic inflammatory disease (PID); an infection of the cervix; an allergy to any component (including copper); or Wilson's disease.
- If a woman misses her period, she must be promptly evaluated for ectopic pregnancy.
- Possible serious complications that have been associated with IUSs are PID, embedment, perforation of the uterus, and expulsion.
- Paragard must not be used by pregnant women as this can be life threatening and may result in loss of pregnancy or infertility.
- Menstrual cycles may become heavier and longer with intermenstrual spotting. Bleeding may be heavier than usual at first.
- **Paragard does not protect against HIV or STIs.**

See next page for Brief Summary of Full Prescribing Information.

Over 6.5 million Paragard units distributed[3]

Paragard® T380A
intrauterine copper contraceptive
simple, honest pregnancy prevention™

CooperSurgical

References: 1. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use; 2017. **2.** Kaneshiro B, Aeby T. Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010;2:211-220. **3.** Data on file. Cooper Surgical, Inc.

*According to the Centers for Disease Control and Prevention (CDC), Paragard is one of the least restrictive birth control options across all patient types compared to other IUSs.

Paragard®
intrauterine copper contraceptive

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR Paragard® T 380A Intrauterine Copper Contraceptive

See package insert for full prescribing information

INDICATIONS AND USAGE

Paragard is indicated for prevention of pregnancy in females of reproductive potential for up to 10 years.

CONTRAINDICATIONS

The use of Paragard is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspicion of pregnancy
- Abnormalities of the uterus resulting in distortion of the uterine cavity
- Acute pelvic inflammatory disease (PID)
- Postpartum endometritis or postabortal endometritis in the past 3 months
- Known or suspected uterine or cervical malignancy
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis or other lower genital tract infection
- Conditions associated with increased susceptibility to pelvic infections
- Wilson's disease
- A previously placed IUD or IUS that has not been removed
- Hypersensitivity to any component of Paragard including copper or any of the trace elements present in the copper component of Paragard

WARNINGS AND PRECAUTIONS

Ectopic Pregnancy

Evaluate for possible ectopic pregnancy in any female who becomes pregnant while using Paragard because a pregnancy that occurs with Paragard in place is more likely to be ectopic than a pregnancy in the general population. However, because Paragard prevents most pregnancies, females who use Paragard have a lower risk of an ectopic pregnancy than sexually active females who do not use any contraception.

The incidence of ectopic pregnancy in the clinical trials with Paragard (which excluded females with a previous history of ectopic pregnancy) was approximately 0.06%. Ectopic pregnancy may require surgery and may result in loss of fertility.

Risks with Intrauterine Pregnancy

If intrauterine pregnancy occurs with Paragard in place and the strings are visible or can be retrieved from the cervical canal, remove Paragard because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of Paragard may also result in spontaneous abortion. In the event of an intrauterine pregnancy with Paragard, consider the following:

Septic Abortion

In females becoming pregnant with an intrauterine system (IUS), including Paragard in place, septic abortion with septicemia, septic shock, and death may occur. Septic abortion typically requires hospitalization and treatment with intravenous antibiotics. Septic abortion may result in spontaneous abortion or a medical indication for pregnancy termination. A hysterectomy may be required if severe infection of the uterus occurs, which will result in permanent infertility.

Continuation of Pregnancy

If a female becomes pregnant with Paragard in place and if Paragard cannot be removed or the female chooses not to have it removed, warn her that failure to remove Paragard increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Prenatal care should include counseling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid, or any other symptom that suggests complications of the pregnancy.

Sepsis

Severe infection or sepsis, including Group A Streptococcal Sepsis (GAS), have been reported following insertion of IUSs, including Paragard. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of Paragard is essential in order to minimize serious infections such as GAS.

Pelvic Inflammatory Disease and Endometritis

Insertion of Paragard is contraindicated in the presence of known or suspected Pelvic Inflammatory Disease (PID) or endometritis. IUSs, including Paragard, have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. In the clinical trials with Paragard, the incidence of PID that resulted in the removal of Paragard was approximately 0.1%.

Counsel women who receive Paragard to notify a healthcare provider if they have complaints of lower abdominal or pelvic pain, odorous discharge, unexplained bleeding, fever, or genital lesions or sores. In such circumstances, perform a pelvic examination promptly to evaluate for possible pelvic infection. Remove Paragard in cases of recurrent PID or endometritis, or if an acute pelvic infection is severe or does not respond to treatment.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and death.

Females at Increased Risk for PID

PID or endometritis are often associated with a sexually transmitted infection (STI) and Paragard does not protect against STIs. The risk of PID or endometritis is greater for females who have multiple sexual partners, and also for females whose sexual partner(s) have multiple sexual partners. Females who have had PID or endometritis are at increased risk for a recurrence or re-infection. In particular, ascertain whether a female is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome (AIDS), intravenous drug abuse).

Asymptomatic PID

PID or endometritis may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID or Endometritis in Patients Using Paragard

Remove Paragard in cases of recurrent endometritis or PID, or if an acute pelvic infection is severe or does not respond to treatment. Prophylactic antibiotics administered at the time of insertion do not appear to lower the incidence of PID.

Promptly assess and treat any female who develops signs or symptoms of PID. Perform appropriate testing for sexually transmitted infection and initiate antibiotic therapy promptly. Paragard does not need to be removed immediately. Reassess the patient in 48-72 hours. If no clinical improvement occurs, continue antibiotics and consider removal of Paragard. If the decision is to remove Paragard, start antibiotics prior to removal to avoid the potential risk for bacterial spread resulting from the removal procedure.

Actinomycosis

Actinomycosis has been associated with IUS use, including Paragard. Symptomatic women with known actinomycosis infection should have Paragard removed and receive antibiotics. Actinomycetes can be found in the genital tract cultures in healthy women without IUSs. The significance of actinomyces-like organisms on a Papanicolaou (PAP) smear in an asymptomatic IUS user is unknown, and this finding alone does not always require IUS removal and treatment. When possible, confirm a PAP smear diagnosis with cultures.

Embedment

Partial penetration of embedment of Paragard in the myometrium can make removal difficult. In some cases, surgical removal may be necessary. Breakage of an embedded Paragard during non-surgical removal has been reported.

Perforation

Partial or total perforation of the uterine wall or cervix may occur during insertions, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. The incidence of perforation during or following Paragard insertion in clinical trials was 0.2% (13 out of 5344).

Delayed detection or removal of Paragard in cases of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal penetration, intestinal obstruction, abscesses and/or damage to adjacent organs.

A postmarketing safety study conducted in Europe (EURAS IUS) with IUSs, including copper IUSs, demonstrated an increased risk of perforation in lactating women. The risk of perforation may be increased if an IUS, such as Paragard, is inserted when the uterus is fixed, retroverted or not completely involuted during the postpartum period.

If perforation does occur, locate and remove Paragard promptly. Surgery may be required. Preoperative imaging followed by laparoscopy or laparotomy is often required to remove Paragard from the peritoneal cavity.

Expulsion

Partial or complete expulsion of Paragard has been reported, resulting in the loss of contraceptive protection. The incidence of expulsion in the clinical trials with Paragard was approximately 2.3%. Consider further diagnostic imaging, such as x-ray, to confirm expulsion if the IUS is not found in the uterus.

Paragard has been placed immediately after delivery, although the risk of expulsion may be increased when the uterus is not completely involuted at the time of insertion. Remove a partially expelled Paragard.

Wilson's Disease

Paragard may exacerbate Wilson's disease, a rare genetic disease affecting copper excretion; therefore, the use of Paragard is contraindicated in females of reproductive potential with Wilson's disease.

Bleeding Pattern Alterations

Paragard can alter the bleeding pattern and result in heavier and longer menstrual cycles with intermenstrual spotting.

In two clinical trials with Paragard, there were reports of oligomenorrhea and amenorrhea; however, a casual relationship between Paragard and these events could not be established. Menstrual changes were the most common medical reason for discontinuation of Paragard. Discontinuation rates for pain and bleeding combined were the highest in the first year of use and diminished thereafter. The percentage of females who discontinued Paragard because of bleeding problems or pain during these studies ranged from 12% in the first year to 2% in year 9. Females complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue Paragard.

Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that Paragard is MR Conditional. A patient with Paragard can be safely scanned in an MR system meeting the following conditions.

- Static magnetic field of 3.0 T or 1.5T
- Maximum spatial gradient of 4,000 gauss/cm (40T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, Paragard is expected to produce a maximum temperature rise of less than 0.58° C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the system extended less than 5mm from the implant when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

Medical Diathermy

Medical equipment that contain high level of Radio-frequency (RF) energy such as diathermy may cause health effects (by heating tissue) in females with a metal-containing IUS including Paragard. Avoid using high medical RF transmitter devices in females with Paragard.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in the Warnings and Precautions:

- Ectopic pregnancy
- Intrauterine pregnancy
- Septic abortion
- Group A Streptococcal Sepsis (GAS)
- Pelvic Inflammatory Disease and Endometritis
- Embedment
- Perforation
- Expulsion
- Bleeding Pattern Alterations

DRUG INTERACTIONS

No drug-drug interaction or drug-herbal supplement interaction studies have been conducted with Paragard.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Use of Paragard is contraindicated for use in pregnant females because there is no need for pregnancy prevention in a female who is already pregnant and Paragard may cause adverse pregnancy outcomes. If a female becomes pregnant with Paragard in place, there is an increased risk of miscarriage, sepsis, premature labor, and premature delivery. Advise the female of the potential risks if pregnancy occurs with Paragard in place.

Published studies on pregnancy outcome exposed to copper IUSs report up to 27% miscarriage when the IUS was removed compared to 77% miscarriage when the IUSs remained in the uterus. Studies on Paragard and birth defects have not been conducted.

Lactation

Risk Summary

No difference has been detected in concentration of copper in human milk before and after insertion of copper IUSs, including Paragard. There is no information on the effect of copper in a breastfed child or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Paragard and any potential adverse effects on the breastfed child from Paragard.

Pediatric Use

The safety and effectiveness of Paragard have been established in females of reproductive potential. Efficacy is expected to be the same for postmenarcheal females regardless of age.

Paragard is not indicated in females before menarche.

Geriatric Use

Paragard has not been studied in women over 65 years of age and is not indicated in this population.

This brief summary is based on the Paragard Full Prescribing Information dated September 2019. The FDA-approved Full Prescribing Information can be found on paragard.com, or call CooperSurgical, Inc. at 1-877-727-2427.

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Infographic: Cardiovascular health among US pregnant women

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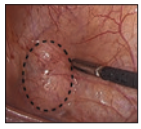

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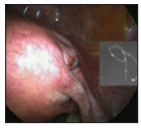

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EDITORIAL

Prescribing aspirin to improve pregnancy outcomes: Expand the indications? Increase the dose?

Low-dose aspirin is effective in reducing the risk of developing preeclampsia. Questions remain about who should be treated and the optimal aspirin dose.

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Authors of a recent Cochrane review concluded that low-dose aspirin treatment of 1,000 pregnant women at risk of developing preeclampsia resulted in 16 fewer cases of preeclampsia, 16 fewer preterm births, 7 fewer cases of small-for-gestational age newborns, and 5 fewer fetal or neonatal deaths.[1]

The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPSTF) recommend treatment with 81 mg of aspirin daily, initiated before 16 weeks of pregnancy to prevent preeclampsia in women with one major risk factor (personal history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal or autoimmune disease) or at least two moderate risk factors (nulliparity; obesity; mother or sister with preeclampsia; a sociodemographic characteristic such as African American race or low socioeconomic status; age ≥35 years; personal history factors such as prior low birth weight infant, previous adverse pregnancy outcome, or >10-year interpregnancy interval).[2,3] Healthy pregnant women with a previous uncomplicated full-term delivery do not need treatment with low-dose aspirin.[2,3]

However, evolving data and expert opinion suggest that expanding the indications for aspirin treatment and increasing the recommended dose of aspirin may be warranted.

Nulliparity

Nulliparity is the single clinical characteristic that is associated with the greatest number of cases of preeclampsia.[4] Hence, from a public health perspective, reducing the rate of preeclampsia among nulliparous women is a top priority.

ACOG and USPSTF do not recommend aspirin treatment for all nulliparous women because risk factors help to identify those nulliparous women who benefit from aspirin treatment.

However, a recent cost-effectiveness analysis compared the health care costs and rates of preeclampsia for 4 prevention strategies among all pregnant women in the United States (nulliparous and parous)[5]:

1. no aspirin use
2. use of aspirin based on biomarker and ultrasound measurements
3. use of aspirin based on USPSTF guidelines for identifying women at risk
4. prescription of aspirin to all pregnant women.

Health care costs and rates of preeclampsia were lowest with the universal prescription of aspirin to all pregnant women in the United States. Compared with universal prescription of aspirin, the USPSTF approach, the biomarker-ultrasound approach, and the no aspirin approach were associated with 346, 308, and 762 additional cases of preeclampsia per 100,000 women. In sensitivity analyses, universal aspirin was the optimal strategy under most assumptions.

Another cost effectiveness analysis concluded that among *nulliparous* pregnant women, universal

aspirin treatment was superior to aspirin treatment based on biomarker-ultrasound identification of women at high risk.[6]

In a recent clinical trial performed in India, Guatemala, Pakistan, Democratic Republic of Congo, Kenya, and Zambia, 14,361 nulliparous women were randomly assigned to placebo or 81 mg of aspirin daily between 6 and 14 weeks of gestation.[7] Preterm birth (<37 weeks' gestation) occurred in 13.1% and 11.6% of women treated with placebo or aspirin (relative risk [RR], 0.89; 95% confidence interval [CI], 0.81 to 0.98, P = .012). Most of the decrease in preterm birth appeared to be due to a decrease in the rate of preeclampsia in the aspirin-treated nulliparous women. The investigators also noted that aspirin treatment of nulliparous women resulted in a statistically significant decrease in perinatal mortality (RR, 0.86) and early preterm delivery, <34 weeks' gestation (RR, 0.75).

Universal prescription of low-dose aspirin to nulliparous women in order to prevent preeclampsia and preterm birth may become recognized as an optimal public health strategy. As a step toward universal prescription of aspirin to nulliparous women, an opt-out rather than a screen-in strategy might be considered.[8]

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Booking systolic blood pressure, 120 to 134 mm Hg

All obstetricians recognize that women with chronic hypertension should be treated with low-dose aspirin because they are at high risk for preeclampsia. However, there is evidence that nulliparous women with a booking systolic pressure ≥120 mm Hg might also benefit from low-dose aspirin treatment. In one US trial, 3,135 nulliparous normotensive women (booking blood pressure [BP] <135/85 mm Hg) were randomly assigned to treatment with aspirin (60 mg daily) or placebo initiated between 13 and 26 weeks' gestation. Preeclampsia occurred in 6.3% and 4.6% of the women treated with placebo or aspirin, respectively (RR, 0.7; 95% CI, 0.6–1.0; P = .05).[9] A secondary analysis showed that, among 519 nulliparous women with a booking systolic BP from 120 to 134 mm Hg, compared with placebo, low-dose aspirin treatment reduced the rate of preeclampsia from 11.9% to 5.6%.[9] Aspirin did not reduce the rate of preeclampsia among nulliparous women with a

TABLE Risks of aspirin treatment[16,a]

Adverse effect	Aspirin group (150 mg daily; n = 798)	Placebo group (n = 822)
Headache and/or dizziness	9.6%	8.8%
Nausea and/or vomiting	5.0%	4.4%
Abdominal and/or pelvic pain	3.3%	4.0%
Vaginal bleeding	3.6%	2.6%
Nasal bleeding	2.0%	3.3%
Gingival, hemorrhoidal, or scleral bleeding and skin bruising	0.9%	0.6%
Anemia	0.5%	0.9%

[a]Reported adverse effects in a clinical trial of 1,776 women treated with aspirin 150 mg or placebo daily, initiated at 11 to 14 weeks' gestation and discontinued at 36 weeks' gestation.

booking systolic BP <120 mm Hg.[9] A systematic review of risk factors for developing preeclampsia reported that a booking diastolic BP of ≥80 mm Hg was associated with an increased risk of developing preeclampsia (RR, 1.38).[10]

The American Heart Association (AHA) and the American College of Cardiology (ACC) recently updated the definition of hypertension.[11] Normal BP is now defined as a systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Elevated BP is a systolic pressure of 120 to 129 mm Hg and diastolic pressure of <80 mm Hg. Stage I hypertension is a systolic BP from 130 to 139 mm Hg or diastolic blood pressure from 80 to 89 mm Hg. Stage II hypertension is a systolic BP of ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.[11]

A recent study reported that 90% of women at 12 weeks' gestation have a BP of ≤130 mm Hg systolic and ≤80 mm Hg diastolic, suggesting that the AHA-ACC criteria for stage I hypertension are reasonable.[12] Obstetricians have not yet fully adopted the AHA-ACC criteria for defining stage I hypertension in pregnant women. Future research may demonstrate that a booking systolic BP ≥130 mm Hg or a diastolic BP ≥80 mm Hg are major risk factors for developing preeclampsia and warrant treatment with low-dose aspirin.

Pregnancy resulting from fertility therapy

Current ACOG and USPSTF guidelines do not specifically identify pregnancies resulting from assisted reproductive technology as a major or moderate risk factor for preeclampsia.[2,3] In a study comparing 83,582 births resulting from in vitro fertilization (IVF) and 1,382,311 births to fertile women, treatment with autologous cryopreserved embryos (adjusted odds ratio [aOR], 1.30), fresh donor embryos (aOR, 1.92), and cryopreserved donor embryos (aOR, 1.70) significantly increased the risk of preeclampsia.[13] However, use of fresh autologous embryos did not increase the risk of preeclampsia (aOR, 1.04). These associations persisted after controlling for diabetes, hypertension, body mass index, and cause of infertility.[13]

Other studies also have reported that use of cryopreserved embryos is associated with a higher rate of preeclampsia than use of fresh autologous embryos. In a study of 825 infertile women undergoing IVF and randomly assigned to single embryo cryopreserved or fresh cycles, the rate of preeclampsia was 3.1% and 1.0% in the pregnancies that resulted from cryopreserved versus fresh cycles.[14]

What is the optimal dose of aspirin?

ACOG and the USPSTF recommend aspirin 81 mg daily for the prevention of preeclampsia.[2,3] The International Federation of Gynecology and Obstetrics (FIGO) recommends aspirin 150 mg daily for the prevention of preeclampsia.[15] The FIGO recommendation is based, in part, on the results of a large international clinical trial that randomly assigned 1,776 women at high risk for preeclampsia as determined by clinical factors plus biomarker and ultrasound screening to receive aspirin 150 mg daily or placebo daily initiated at 11 to 14 weeks' gestation and continued until 36 weeks' gestation.[16] Preeclampsia before 37 weeks' gestation occurred in 4.3% and 1.6% of women in the placebo and aspirin groups (OR, 0.38; 95% CI, 0.20–0.74; P = .004).[16] FIGO recommends that women at risk for preeclampsia with a body mass <40 kg take aspirin 100 mg daily and women with a body mass ≥40 kg take aspirin at a dose of 150 mg daily. For women who live in a country where aspirin is not available in a pill containing 150 mg, FIGO recommends taking two 81 mg tablets.[15] FIGO recommends initiating aspirin between 11 and 14 weeks and 6 days of gestation and continuing aspirin therapy until 36 weeks of gestation.[15]

Aspirin is an inexpensive intervention with many possible benefits

For many nulliparous women and some parous women aspirin treatment initiated early in pregnancy will improve maternal and newborn outcomes, including reducing the risk of preeclampsia, preterm birth, and intrauterine growth restriction.[1] Obstetricians may want to begin to expand the indications for offering aspirin to prevent preeclampsia from those recommended by ACOG and the USPSTF to include nulliparous women with a booking systolic pressure of 120 to 134 mm Hg and women whose pregnancy was the result of an assisted reproduction treatment that used cryopreserved embryos. In addition, obstetricians who currently prescribe 81 mg of aspirin daily might want to consider increasing the prescribed dose to 162 mg of aspirin daily (two 81 mg tablets daily or one-half of a 325 mg tablet). Aspirin costs about less than 5 cents per 81 mg tablet (according to GoodRx website). It is an inexpensive intervention that could benefit many mothers and newborns. ●

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Dr. Barbieri reports no financial relationships relevant to this article.

CONTINUED ON PAGE 14

FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS DUE TO MENOPAUSE IN WOMEN WITH A UTERUS

PRECISELY COMBINED[1]

Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

BIJUVA IS THE FIRST AND ONLY FDA-APPROVED COMBINATION OF

BIO-IDENTICAL* ESTROGEN + MICRONIZED PROGESTERONE

IN A SINGLE ONCE-DAILY ORAL CAPSULE[1-3]

*Bio-identical hormones are structurally identical to the hormones produced within a woman's body. The relevance of risks associated with the use of synthetic hormones compared to bio-identical hormones is not known but cannot be excluded.

TO REQUEST SAMPLES, VISIT BIJUVAINFO.COM

INDICATION

BIJUVA is a combination of estradiol and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer**
- **The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older**

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The WHI estrogen-alone substudy reported increased risks of stroke and DVT**
- **The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older**

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, therapy should be discontinued immediately. Risk factors for arterial vascular disease and/or venous thromboembolism (VTE) should be managed appropriately.
- The WHI substudy of daily estrogen plus progestin after a mean follow-up of 5.6 years reported an increased risk of invasive breast cancer. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy after several years of use. The risk increased with duration of use and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). The use of estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- Endometrial hyperplasia (a possible precursor to endometrial cancer) has been reported to occur at a rate of approximately less than one percent with BIJUVA. Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin when compared to placebo. It is unknown whether these findings apply to younger postmenopausal women.
- Estrogens increase the risk of gallbladder disease.
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.
- Monitor thyroid function in women on thyroid replacement hormone therapy.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) for BIJUVA are breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

Please note that this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following pages.

References: 1. BIJUVA [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019. **2.** Lobo RA, Liu J, Stanczyk FZ, et al. Estradiol and progesterone bioavailability for moderate to severe vasomotor symptom treatment and endometrial protection with the continuous-combined regimen of TX-001HR (oral estradiol and progesterone capsules). *Menopause.* 2019;26(7):720-727. **3.** Lobo RA, Archer DF, Kagan R, et al. A 17ß-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol.* 2018;132(1):161-170.

TherapeuticsMD®
For Her. For Life.

BIJUVA® (estradiol and progesterone) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use **BIJUVA** safely and effectively. Please visit BIJUVAHCP.com for Full Prescribing Information.

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5) in full prescribing information].*

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4) in full prescribing information].*

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].*

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.4) in full prescribing information].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

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

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2) in full prescribing information].*

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5) in full prescribing information].*

The WHI estrogen-alone substudy reported increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4) in full prescribing information].*

The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

DOSAGE AND ADMINISTRATION

Use of estrogen, alone or in combination with a progestogen, should be limited to the lowest effective dose available and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be reevaluated periodically as clinically appropriate to determine if treatment is still necessary.

Take a single BIJUVA (estradiol and progesterone) capsule, 1 mg/100 mg, orally each evening with food.

CONTRAINDICATIONS

BIJUVA is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, MI), or a history of these conditions
- Known anaphylactic reaction, angioedema, or hypersensitivity to BIJUVA or any of its ingredients
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should these occur or be suspected, therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women's Health Initiative estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.4) in full prescribing information]*. The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.4) in full prescribing information]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.4) in full prescribing information]*.

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo *[see Clinical Studies (14.4) in full prescribing information]*.

Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated.

The increase in VTE risk was demonstrated during the first year and persisted *[see Clinical Studies (14.4) in full prescribing information]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years [*see Clinical Studies (14.4) in full prescribing information]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups *[see Clinical Studies (14.4) in full prescribing information]*.

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80] *[see Clinical Studies (14.4) in full prescribing information]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

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

In a one-year trial, among 1,684 women who received a combination of estradiol plus progesterone (1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 415 women treated with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 151 women treated with placebo.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

(continued on next page)

Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestogen to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95% confidence interval [CI], 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% CI, 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years *[see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information]*.

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

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

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestogen with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Estrogens and progestins may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens plus progestins are prescribed.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Exacerbation of Other Conditions

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

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reactions with BIJUVA (incidence ≥ 3% of women and greater than placebo) were breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

BIJUVA is not indicated for use in pregnancy. There are no data with the use of BIJUVA in pregnant women, however, epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) before conception or during early pregnancy.

Lactation

BIJUVA is not indicated for use in females of reproductive potential. Estrogens are present in human milk and 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.

Pediatric Use

BIJUVA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing BIJUVA to determine whether those over 65 years of age differ from younger women in their response to BIJUVA.

An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative

OVERDOSAGE

Overdosage of estrogen plus progestogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of BIJUVA therapy with institution of appropriate symptomatic care.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for: TherapeuticsMD, Inc. Boca Raton, FL 33431
Based on BJVA-LAB-20003.4 Revised: 11/2019

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CONTINUED FROM PAGE 10

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Do ObGyns think hormonal contraception should be offered over the counter?

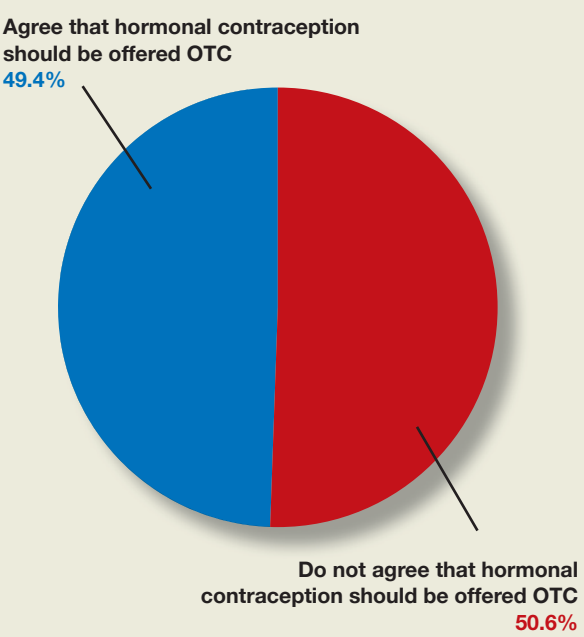
In their advocacy column, "OTC hormonal contraception: An important goal in the fight for reproductive justice" (January 2020), Abby L. Schultz, MD, and Megan L. Evans, MD, MPH, discussed a recent committee opinion from the American College of Obstetricians and Gynecologists (ACOG) focused on improving contraception access by offering oral contraceptive pills, progesterone-only pills, the patch, vaginal rings, and depot medroxyprogesterone acetate over the counter (OTC). The authors agreed with ACOG's stance and offered several reasons why.

OBG MANAGEMENT polled readers to see their thoughts on the question of whether or not hormonal contraception should be offered OTC.

Poll results

A total of 166 readers cast their vote:

- **50.6% (84 readers)** said no
- **49.4% (82 readers)** said yes



Enhancing patient outcomes, managing costs, and optimizing quality of life.

The value of care:

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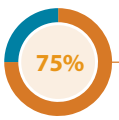
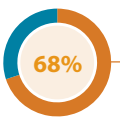
About **ONE** in **TWO** sexually active people will acquire an STI by **AGE 25.**

Infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are commonly asymptomatic.



~75% of women infected with **chlamydia** are asymptomatic[1]



~68% of women infected with **gonorrhea** are asymptomatic[1]

Chlamydia and gonorrhea are two of the most common reportable sexually transmitted infections (STIs) and rates of infection are on the rise.

A universal screening CT/NG strategy would focus on women within the high-risk age group covered by guidelines from USPSTF and CDC guidelines (women 15-24 years old) without regard to the sexual activity they report.

Universal screening may help to:[2]

- Decrease STI prevalence
- Decrease infertility due to undiagnosed infections
- Reduce health care cost

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Can a drug FDA approved for endometriosis become a mainstay for nonsurgical treatment of HMB in women with fibroids?

Elagolix is a GnRH antagonist that is approved in a 2-dose schedule for treatment of endometriosis. It is given orally and, as expected and clearly shown by the investigators in two identical, double-blind, randomized, placebo-controlled phase 3 trials, **significantly reduces heavy menstrual bleeding (HMB) in women with fibroids**. Because previous studies showed an increase in vasomotor symptoms and some negative impact on bone metabolism with elagolix, these studies, in addition to a placebo arm, included one arm with elagolix alone and one arm with "add-back therapy" that utilized estradiol and norethindrone acetate. The add-back therapy attenuated the hypoestrogenic effects of elagolix.

FAST TRACK

Elagolix plus add-back therapy will allow for greater patient acceptance of the GnRH antagonist

Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl J Med. 2020;382:328-340.

EXPERT COMMENTARY

Steven R. Goldstein, MD, is Professor, Obstetrics and Gynecology, New York University School of Medicine, and Director of Gynecologic Ultrasound and Co-Director of Bone Densitometry, NYU Langone Medical Center, New York. He serves on the OBG MANAGEMENT Board of Editors.

Any women's health care provider is extremely aware of how common uterine fibroids (leiomyomas) are in reproductive-aged women. Bleeding associated with such fibroids is a common source of medical morbidity and reduced quality of life for many patients. The mainstay treatment approach for such patients has been surgical, which over time has become minimally invasive. Finding a nonsurgical treatment for patients with fibroid-associated HMB is of huge importance. The recent failure of the selective progesterone receptor modulator ulipristal acetate to be approved by the US Food and Drug Administration (FDA) was a significant setback to finding an excellent option for medical management. A gonadotropin-releasing hormone (GnRH) antagonist like elagolix could become an incredibly important "arrow in the quiver" of women's health clinicians.

The author reports being an advisory board member for AbbVie Inc.

Details about elagolix

As mentioned, elagolix was FDA approved in 2-dose regimens for the treatment of dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia associated with endometriosis. One would expect that such a GnRH antagonist would reduce or eliminate HMB in patients with fibroids, although formal study had never been undertaken. Previous studies of elagolix had shown the most common adverse reaction to be vasomotor symptoms—hot flashes and night sweats. In addition, the drug shows a dose-dependent decrease in bone mineral density (BMD), although its effect on long-term bone health and future fracture risk is unknown.[1]

Study specifics. The current study by Schlaff and colleagues was performed including 3 arms: a placebo arm, an elagolix 300 mg twice daily arm, and a third arm that received elagolix 300 mg twice daily and hormonal "add-back" therapy in the form of estradiol 1 mg and norethindrone acetate 0.5 mg daily. The authors actually report on two phase 3 six-month trials that were identical, double-blind, and randomized in nature. Both trials involved approximately 400 women. About 70% of the study participants overall were black, and the average age was approximately 42 years (range, 18 to 51). At baseline, BMD scores were mostly in the normal range. HMB for inclusion was defined as a volume of more than 80 mL per month.

The primary end point was menstrual blood loss volume less than 80 mL in the final month and at least a 50% reduction in menstrual blood loss from baseline to the final month. In the placebo group, only 9% and 10%, respectively, met these criteria.

Results. In the first study group, 84% of those receiving elagolix alone achieved the primary end point, while the group that received elagolix plus add-back therapy had 69% success.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Elagolix is currently available (albeit not in the dosing regimen used in the current study or with built-in add-back therapy), and these study results offer an encouraging nonsurgical approach to HMB. The addition of add-back therapy to this oral GnRH antagonist will allow greater patient acceptance from a quality-of-life point of view because of diminution of vasomotor symptoms while maintaining BMD.

STEVEN R. GOLDSTEIN, MD

In the second study, both the elagolix group and the add-back group showed that 77% of patients met the primary end point criteria.

The incidences of hot flashes in the elagolix-alone groups were 64% and 43%, respectively, while with add-back therapy, they were 20% in both trials. In the placebo groups, 9% and 4% of participants reported hot flashes. At 6 months, the elagolix-only groups in both trials lost more BMD than the placebo groups, while BMD loss in both add-back groups was not statistically significant from the placebo groups.

Study strengths

Schlaff and colleagues conducted a very well-designed study. The two phase 3 clinical trials in preparation for drug approval were thorough and well reported. The authors are to be commended for including nearly 70% black women as study participants, since this is a racial group known to be affected by HMB resulting from fibroids.

Another strength was the addition of add-back therapy to the doses of elagolix. Concerns about bone loss from a health perspective and vasomotor symptoms from a quality-of-life perspective are not insignificant with elagolix-alone treatment, and proof that add-back therapy significantly diminishes or attenuates the efficacy of this entity is extremely important. ●

FAST TRACK

Add-back therapy reduced the incidences of hot flashes from 64% and 43% to 20% and 20%, respectively

Reference

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UPDATE Prenatal phenotyping

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The authors report no financial relationships relevant to this article.

In prenatal phenotyping, understanding standardization of language, specific prenatal descriptions, and artificial intelligence may contribute toward the making of a diagnosis

As prenatal genetic testing and imaging have advanced, the diagnosis of genetic disorders has moved from the postnatal to the prenatal time frame. This has largely been facilitated by the increasing use of exome sequencing (ES) in the prenatal setting. Two landmark trials published in January 2019 highlighted the overall diagnostic yields of prenatal ES as 8.5% and 10% in fetuses with normal karyotype and microarray.[1,2]

Although this is a huge step forward in prenatal diagnosis, ES is currently a manually curated, labor-intensive task. The process involves reviewing thousands of sequence variants for any given sample and prioritizing each variant based on bioinformatic data, prediction models, literature review, and specific patient characteristics. The patient characteristics, or phenotypic information, are critically important in prioritizing candidate variants.

To date, prenatal ES has been limited by the use of inconsistent terminology and the lack of well-understood prenatal phenotypes. In this Update, we highlight how recently published work draws attention to these critical gaps in prenatal diagnosis.

IN THIS ARTICLE

Standardizing phenotyping language in the prenatal setting

Tomar S, Sethi R, Lai PS. Specific phenotype semantics facilitate gene prioritization in clinical exome sequencing. Eur J Hum Genet. 2019;27:1389-1397.

Clinical ES in pediatric and adult populations is enhanced by the use of standardized vocabulary to describe disorders. Standardized language ensures that identified variants are filtered correctly and in a systematic fashion based on the patient characteristics that are provided. One commonly used platform is the Human Phenotype Ontology (HPO).

Tomar and colleagues assessed the impact of HPO-based clinical information on the performance of a gene prioritization tool.[3] Gene prioritization (or simulation) tools are used for interpretation of ES data to help analysts efficiently sort through the thousands of variants in an individual's genetic sequence. The performance, or accuracy, of a prioritization tool can be assessed

by looking at the location of the disease-causing gene in the suggested gene list.

Cohort of diagnosed patients and gene prioritization

In this experimental model, Tomar and colleagues included 50 cases with neuromuscular disorders; all had available sequencing data, fully described phenotypes, and known causal genes. The authors varied the level of available clinical information in the HPO terms used for simulated variant analysis. Using 3 web-based gene prioritization tools on the 50 cases, they varied the HPO input to include a random selection of 10%, 30%, and 50% of HPO terms derived from deep phenotyping.

The 3 prioritization tools ranked input genes based on gene-phenotype associations that were derived from gene-phenotype databases. The authors then assessed the quality of the candidate gene lists by the location of the known causative gene on the generated rank lists. They repeated this analysis 4 times with different randomly selected HPO terms.

Inclusion of more HPO terms allowed for more accurate diagnoses in rare disorders

The authors found that the phenotype input for ES matters. When only 10% and 30% of the HPO terms were used to create a candidate gene list, the causative gene was less likely to be in the top portions of gene lists than when 50% or 100% of the available HPO terms were used.

For well-characterized disorders, use of the top 10% HPO terms performed as well as when all available HPO terms were used. For previously undescribed disease-gene associations, identification of the disease gene suffered with more limited HPO term availability.

What this study contributes

This study was a simulation of previously sequenced patients with neuromuscular disorders. It examined a small sample size for a narrow spectrum of disease. However, it clearly illustrated the principle that completeness of phenotypic information for ES pipelines is relevant for interpretation.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The quantity and quality of phenotype input into ES matters for assessing genetic variants. HPO terms have been developed to represent prenatal sonographic findings, and these have been extended to include gestational age of onset in some cases. Providing as much data as possible about the prenatal phenotype through accepted uniform vocabulary (such as HPO) will increase the likelihood that a prenatal diagnosis can be made.

FAST TRACK

When only 10% and 30% of the HPO terms were used to create a candidate gene list, the causative gene was less likely to be in the top portions of gene lists than when 50% or 100% of the available HPO terms were used

Detailed description of prenatal findings is essential to diagnosis

Aarabi M, Sniezek O, Jiang H, et al. Importance of complete phenotyping in prenatal whole exome sequencing. Hum Genet. 2018;137:175-181.

In a retrospective cohort study, Aarabi and colleagues evaluated the diagnostic utility and limitations of ES in prenatal cases with structural birth defects.[4]

A case series study

The investigators included 20 pregnancies with structural birth defects that were referred to their center for prenatal diagnosis between 12 and 20 weeks' gestation. All pregnancies had normal karyotype and microarray analyses prior to enrollment.

ES was performed on trio samples, which included fetal and parental DNA

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Prenatal genetic diagnosis often is limited by incomplete information about the features seen on ultrasonography. Although not all features are visible prenatally, more diagnoses can be made if laboratories are provided with detailed information about the structural abnormalities that are seen. Furthermore, if ES does not provide a prenatal diagnosis, the data should be reviewed postnatally if more detailed phenotypic information becomes available.

samples (extracted from peripheral blood). Reports provided by the commercial laboratories were normal for all cases and included no pathogenic or likely pathogenic variants. The laboratory provided the investigators with the FASTQ (genetic sequence) files for reanalysis, which was performed using both prenatal and postnatal detailed phenotypic information.

FAST TRACK

Although not all features are visible prenatally, more diagnoses can be made if laboratories are given detailed information about the structural abnormalities that are seen

Use of postnatal information facilitated diagnoses

Reanalysis of ES data using detailed postnatal findings revealed a possible diagnosis in 20% of cases. Each case in which a diagnosis was made, detailed below, highlights an important limitation in our current ability to make prenatal diagnoses.

Case 1. A fetus was diagnosed prenatally with arthrogryposis, plagiocephaly, and club feet. After birth, the infant also was found to have generalized muscle weakness, elevated creatine phosphokinase, and congenital hip dislocation.

Reanalysis of the ES data revealed compound heterozygous missense variants in the nebulin gene (*NEB*). Although classified as variants of uncertain significance (VUS), these are consistent with the phenotype, the authors argued, and with the diagnosis of autosomal recessive nemaline myopathy 2.

Case 2. Prenatal diagnosis was made of a right limb anomaly, tetralogy of Fallot, intrauterine growth restriction, ambiguous genitalia, and dextrocardia. Postnatal evaluation revealed absent pulmonary valve syndrome, right arm dysplasia, pectus carinatum deformity, and failure to thrive.

In this case, ES with the postnatal information revealed a VUS in the *NOTCH1* gene, which has been associated with Adams-Oliver syndrome. Although by strict criteria this variant is also of uncertain significance, Adams-Oliver syndrome is characterized, in part, by transverse limb defects and congenital heart disease, as was found in the proband.

Case 3. Prenatal ultrasonography revealed microcephaly and absence of the septum pellucidum. Postnatal magnetic resonance imaging revealed semi-lobar holoprosencephaly. A holoprosencephaly-specific gene panel revealed a deletion in the *ZIC2* gene, which is known to cause holoprosencephaly.

Careful re-examination of the ES data revealed some abnormality in the *ZIC2* signal, which might have been studied in greater detail and thereby detected if the prenatal diagnosis of holoprosencephaly had been made.

Case 4. An ultrasound evaluation at 12 weeks' gestation revealed a cystic hygroma, short long bones, and possible absent hand and fibula. A postnatal fetal autopsy at 14 weeks showed split-hand and split-foot malformations, which were not appreciated on ultrasonography.

In filtering the ES data with this information, a pathogenic variant in the *PRCN* gene was identified as causal, and the diagnosis of Goltz syndrome was made.

Challenges facing prenatal diagnosis

A case series is inherently limited by its small sample size. Nevertheless, the authors suggest 2 major challenges in our ability to make the above diagnoses in the prenatal setting: 1) the prenatal assessment being limited to major structural abnormalities, and 2) commercial laboratories not having enough experience or volume to interpret the limited information provided by prenatal imaging.

CONTINUED ON PAGE 23

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CONTINUED FROM PAGE 20

Can AI technology be incorporated to make a genetic diagnosis?

Hsieh TC, Mensah MA, Pantel JT, et al. PEDIA: prioritization of exome data by image analysis. Genet Med. 2019;21:2807-2814.

Increasingly, ES is used in all types of undiagnosed, rare genetic diseases. Although there is a high diagnostic yield in many populations, ES's clinical utility is limited by the labor-intensive process of interpreting each variant in the context of detailed phenotypic information. The widespread use of HPO would be one step toward standardizing the information that is entered into the analysis of ES data, but even HPO cannot capture certain visual clues.

Hsieh and colleagues attempted to use artificial intelligence (AI) for "next-generation phenotyping" to assess facial dysmorphology and integrate the information into variant classification.[5] The authors described their approach of incorporating AI as "prioritization of exome data by image analysis" (PEDIA).

Designing dysmorphology machine learning

The cohort included 679 individuals with 105 different genetic disorders. All individuals had a previously confirmed molecular diagnosis that would be detected by ES. Each individual had a frontal facial photograph analyzed and detailed clinical features documented in HPO terms extracted by 2 clinicians.

A facial analysis software called DeepGestalt, trained on 17,000 patient images, was used to create a Gestalt score. Each individual had 4 different predicted gene scoring approaches:

- a molecular deleteriousness score
- facial analysis with the Gestalt score
- a combination of molecular deleteriousness score and HPO-based gene-prioritization tool (termed semantic similarity score)
- the PEDIA score, which included all 3 prior approaches.

A type of machine learning algorithm (support vector machine, or SVM) was applied, validated, and used to prioritize genes based on the combined scores.

AI seemed to improve diagnostic accuracy

Utilizing the combination of machine learning, HPO terms, and facial analysis software greatly improved the accuracy of variant classification predictions over any approach alone.

Using only the sequence variant and molecular deleteriousness score, the causative variant was ranked in the top 10 of all identified variants in less than 45% of cases. Adding the HPO-based gene prioritization tools increased the accuracy to 63% to 94%. Use of the PEDIA score, which incorporated all 3, increased the accuracy to 99% for the top 10 ranking.

Even more impressive improvements were made in the top 1 ranking accuracy rate, which went from 36% to 74% without facial image information to 86% to 89% with inclusion of DeepGestalt scores.

Study strengths and limitations

This study's innovative application of facial analysis and machine learning, combined with

FAST TRACK

The combination of machine learning, HPO terms, and facial analysis software greatly improved the accuracy of variant classification predictions over any approach alone

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The accuracy of gene prediction in pediatric and adult populations is enhanced by the use of computer-assisted image analysis and machine-learning algorithms. These computational methods may be employed to automate variant classification, making it more accurate, efficient, and less laborious. Detailed descriptions or characteristic images of prenatal findings also may allow this technology to be introduced in the prenatal setting.

HPO-driven variant classification, showed added benefit. To achieve this with available patient photographs and thorough phenotyping, previously diagnosed patients were used. Because complete ES information was not available for those patients, their known pathogenic variant was inserted into randomly selected exomes from the 1000 Genomes Project (healthy individuals). The authors additionally noted that the PEDIA score performance was diminished for rare disorders in which limited data were available. ●

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Haley Letter, MD; Andrew M. Kaunitz, MD; and Bharti Jasra, MBBS

IN THIS ARTICLE

CASE Young woman with discharge from one nipple

A 26-year-old African American woman presents with a 10-month history of left nipple discharge. The patient describes the discharge as spontaneous, colored dark brown to yellow, and occurring from a single opening in the nipple. The discharge is associated with left breast pain and fullness, without a palpable lump. The patient has no family or personal history of breast cancer.

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Nipple discharge is the third most common breast-related symptom (after palpable masses and breast pain), with an estimated prevalence of 5% to 8% among premenopausal women.[1] While most causes of nipple discharge reflect benign issues, approximately 5% to 12% of breast cancers have nipple discharge as the only symptom.[2] Not surprisingly, nipple discharge creates anxiety for both patients and clinicians.

In this article, we—a breast imaging radiologist, gynecologist, and breast surgeon—outline key steps for evaluating and managing patients with nipple discharge.

Two types of nipple discharge

Nipple discharge can be characterized as physiologic or pathologic. The distinction is based on the patient's history in conjunction with the clinical breast exam.

Physiologic nipple discharge often is bilateral, nonspontaneous, and white, yellow, green, or brown (**TABLE**).[3] It often is due to nipple stimulation, and the patient can elicit discharge by manually manipulating the breast. Usually, multiple ducts are involved. *Galactorrhea* refers specifically to milky discharge and occurs most commonly during pregnancy or lactation.[2] Galactorrhea that is not associated with pregnancy or lactation often is related to elevated prolactin or thyroid-stimulating hormone levels or to medications. One study reported that no cancers

TABLE Characteristics of physiologic and pathologic nipple discharge[3]

Pathologic	Physiologic
Bloody	Bilateral
Clear	Nonspontaneous
Spontaneous	Milky, green, yellow, brown
Unilateral	Negative physical exam
Palpable breast mass	
Skin changes/nipple retraction	

were found when discharge was nonspontaneous and colored or milky.[4]

Pathologic nipple discharge is defined as a spontaneous, bloody, clear, or single-duct discharge. A palpable mass in the same breast automatically increases the suspicion of the discharge, regardless of its color or spontaneity.[2] The most common cause of pathologic nipple discharge is an intraductal papilloma, a benign epithelial tumor, which accounts for approximately 57% of cases.[5]

Although the risk of malignancy is low for all patients with nipple discharge, increasing age is associated with increased risk of breast cancer. One study demonstrated that among women aged 40 to 60 years presenting with nipple discharge, the prevalence of invasive cancer is 10%, and the percentage jumps to 32% among women older than 60.[6]

Breast exam. For any patient with nonlactational nipple discharge, we recommend a thorough breast examination. Deep palpation of all quadrants of the symptomatic breast, especially near the nipple areolar complex, should elicit nipple discharge without any direct squeezing of the nipple. If the patient's history and physical exam are consistent with physiologic discharge, no further workup is needed. Reassure the patient and recommend appropriate breast cancer screening. Encourage the patient to decrease stimulation or manual manipulation of the nipples if the discharge bothers her.

CASE Continued: Workup

On physical exam, the patient's breasts are noted to be cup size DDD and asymmetric, with the left breast larger than the right; there is no contour deformity. There is no skin or nipple retraction, skin rash, swelling, or nipple changes bilaterally. No dominant masses are appreciated bilaterally. Manual compression elicits no nipple discharge.

Although the discharge is nonbloody, its spontaneity, unilaterality, and single-duct/orifice origin suggest a pathologic cause. The patient is referred for breast imaging.

Imaging workup for pathologic discharge

The American College of Radiology (ACR) Appropriateness Criteria is a useful tool that provides an evidence-based, easy-to-use algorithm for breast imaging in the patient with pathologic nipple discharge (**FIGURE 1,** page 28).[6] The algorithm is categorized by patient age, with diagnostic mammography recommended for women aged 30 and older.[6] Diagnostic mammography is recommended if the patient has not had a mammogram study in the last 6 months.[6] For patients with no prior mammograms, we recommend bilateral diagnostic mammography to compare symmetry of the breasts.

Currently, no studies show that digital breast tomosynthesis (3-D mammography) has a benefit compared with standard 2-D mammography in women with pathologic nipple discharge.[6] Given the increased sensitivity of digital breast tomosynthesis for cancer detection, however, in our practice it is standard to use tomosynthesis in the diagnostic evaluation of most patients.

Mammography

On mammography, ductal carcinoma in situ (DCIS) usually presents as calcifications.

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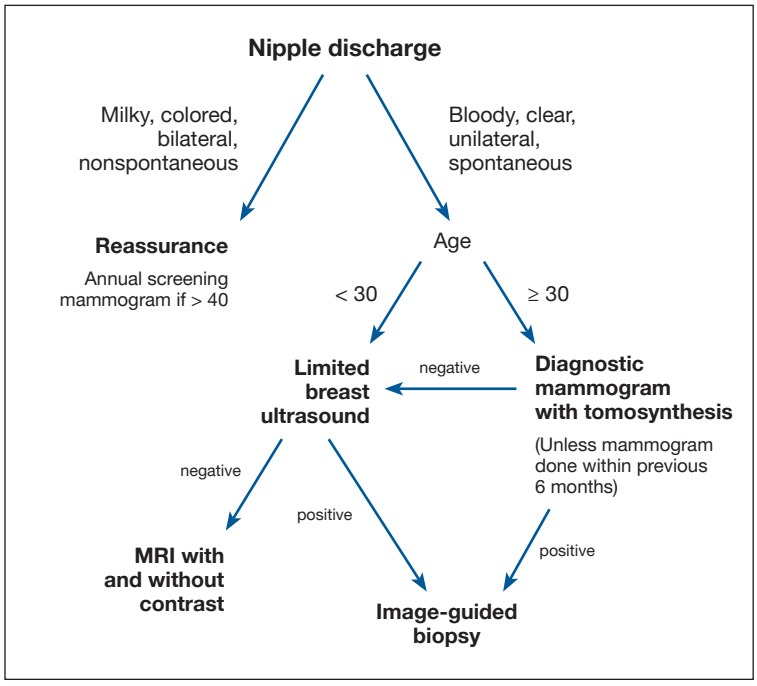

FIGURE 1 Algorithm for diagnostic imaging based on nipple discharge characteristics and patient age[6]

Both the morphology and distribution of calcifications are used to characterize them as suspicious or, typically, benign. DCIS usually presents as fine pleomorphic or fine linear branching calcifications in a segmental or linear distribution. In patients with pathologic nipple discharge and no other symptoms, the radiologist must closely examine the retroareolar region of the breast to assess for faint calcifications. Magnification views also can be performed to better characterize calcifications.

The sensitivity of mammography for nipple discharge varies in the literature, ranging from approximately 15% to 68%, with a specificity range of 38% to 98%.[6] This results in a relatively low positive predictive value but a high negative predictive value of 90%.[7] Mammographic sensitivity largely is limited by increased breast density. As more data emerge on the utility of digital breast tomosynthesis in dense breasts, mammographic sensitivity for nipple discharge will likely increase.

Ultrasonography

As an adjunct to mammography, the ACR Appropriateness Criteria recommends targeted (or "limited") ultrasonography of the retroareolar region of the affected breast for patients aged 30 and older. Ultrasonography is useful to assess for intraductal masses and architectural distortion, and it has higher sensitivity but lower specificity than mammography. The sensitivity of ultrasonography for detecting breast cancer in patients presenting with nipple discharge is reported to be 56% to 80%.[6] Ultrasonography can identify lesions not visible mammographically in 63% to 69% of cases.[8] Although DCIS usually presents as calcifications, it also can present as an intraductal mass on ultrasonography.

The ACR recommends targeted ultrasonography for patients with nipple discharge and a negative mammogram, or to evaluate a suspicious mammographic abnormality such as architectural distortion, focal asymmetry, or a mass.[6] For patient comfort, ultrasonography is the preferred modality for image-guided biopsy.

For women younger than 30 years, targeted ultrasonography is the initial imaging study of choice, according to the ACR criteria.[6] Women younger than 30 years with pathologic nipple discharge have a very low risk of breast cancer and tend to have higher breast density, making mammography less useful. Although the radiation dose from mammography is negligible given technological improvements and dose-reduction techniques, ultrasonography remains the preferred initial imaging modality in young women, not only for nipple discharge but also for palpable lumps and focal breast pain.

Mammography is used as an adjunct to ultrasonography in women younger than 30 years when a suspicious abnormality is detected on ultrasonography, such as an intraductal mass or architectural distortion. In these cases, mammography can be used to assess for extent of disease or to visualize suspicious calcifications not well seen on ultrasonography.

For practical purposes regarding which imaging study to order for a patient, it is most efficient to order both a diagnostic mammogram (with tomosynthesis, if possible) and a

targeted ultrasound scan of the affected breast. Even if both orders are not needed, having them available increases efficiency for both the radiologist and the ordering physician.

CASE Continued: Imaging findings

Given her age, the patient initially undergoes targeted ultrasonography. The grayscale image (**FIGURE 2**) demonstrates multiple mildly dilated ducts (white arrows) with surrounding hyperechogenicity of the fat (red arrows), indicating soft tissue edema. No intraductal mass is imaged. Given that the ultrasonography findings are not completely negative and are equivocal for malignancy, bilateral diagnostic mammography (**FIGURE 3**, left breast only) is performed. Standard full-field craniocaudal (**FIGURE 3A**) and mediolateral oblique (**FIGURE 3B**) mammographic views demonstrate a heterogeneously dense breast with a few calcifications in the retroareolar left breast (red ovals). No associated mass or architectural distortions are noted. The mammographic and sonographic findings do not reveal a definitive biopsy target.

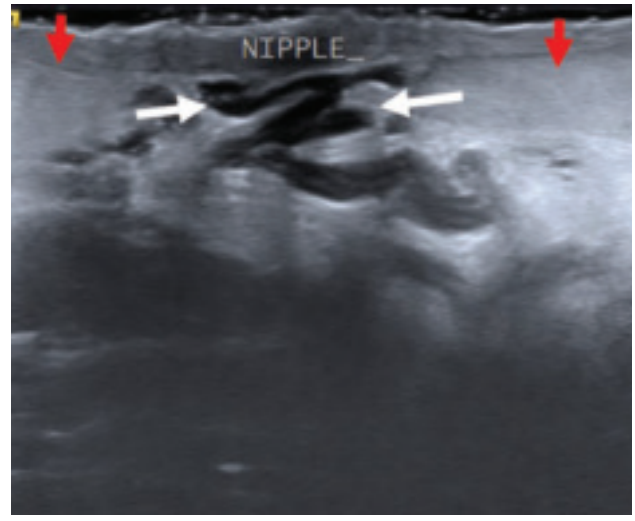

FIGURE 2 Ultrasonographic grayscale image of the left breast shows mildly dilated ducts (white arrows) with surrounding hyperechogenicity of the fat (red arrows) indicating soft tissue edema

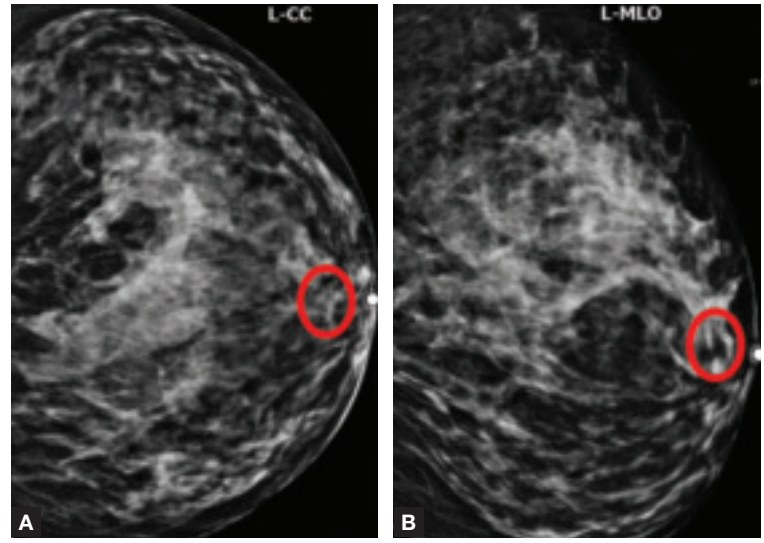

FIGURE 3 Standard full-field craniocaudal (**A**) and mediolateral oblique (**B**) mammographic views show heterogeneously dense breast tissue with a few calcifications in the retroareolar left breast (red ovals)

Ductography

When a suspicious abnormality is visualized on either mammography or ultrasonography, the standard of care is to perform an image-guided biopsy of the abnormality. When the standard workup is negative or equivocal, the standard of care historically was to perform ductography.

Ductography is an invasive procedure that involves cannulating the suspicious duct with a small catheter and injecting radiopaque dye into the duct under mammographic guidance. While the sensitivity of ductography is higher than that of both mammography and ultrasonography, its specificity is lower than that of either modality.

Most cases of pathologic discharge are spontaneous and are not reproducible on the day of the procedure. If the procedural radiologist cannot visualize the duct that is producing the discharge, the procedure cannot be performed. Although most patients tolerate the procedure well, ductography produces patient discomfort from cannulation of the duct and injection of contrast.

Magnetic resonance imaging

Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the most sensitive imaging study for evaluating pathologic nipple discharge, and it has largely replaced ductography as an adjunct to mammography and ultrasonography. MRI's sensitivity for detecting breast cancer ranges from 93% to 100%.[6] In addition, MRI allows visualization of the entire breast and areas peripheral to

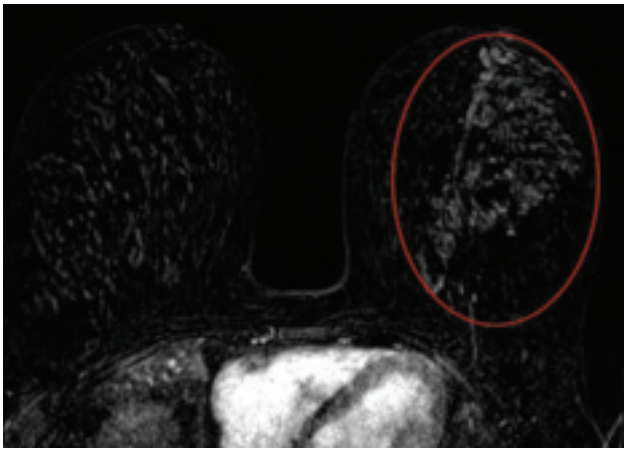

FIGURE 4 Contrast-enhanced magnetic resonance imaging of the breasts demonstrates an area of non-mass enhancement (red oval) in the left breast extending from the nipple to the posterior breast tissue

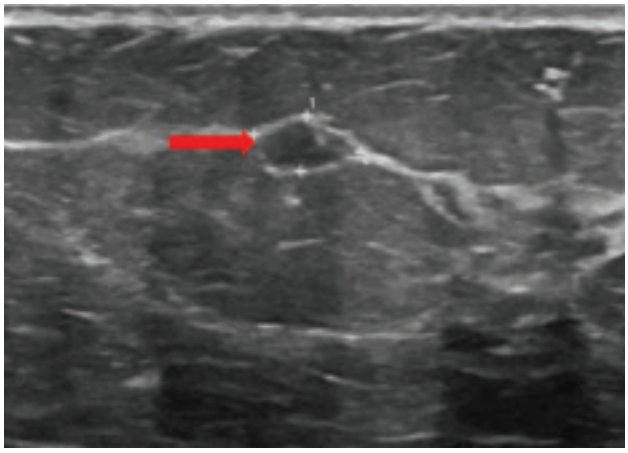

FIGURE 5 Magnetic resonance imaging-directed ultrasound scan of the left breast reveals a small irregular mass at the 1 o'clock position, 10-11 cm from the nipple (red arrow)

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Once the pathology report from the image-guided biopsy is available, the radiologist makes a radiologic-pathologic concordance statement and recommends surgical consultation. This allows the surgeon to have all needed information at the initial visit.

the field of view of a standard ductogram or ultrasound scan.[9]

Clinicians commonly ask, "Why not skip the mammogram and ultrasound scan and go straight to MRI, since it is so much more sensitive?" Breast MRI has several limitations, including relatively low specificity, cost, use of intravenous contrast, and patient discomfort (that is, claustrophobia, prone positioning). MRI should be utilized for pathologic discharge only when the mammogram and/or targeted ultrasound scans are negative or equivocal.

CASE Continued: Additional imaging

A contrast-enhanced MRI of the breasts (**FIGURE 4**) demonstrates a large area of non-mass enhancement (red oval) in the left breast, which involves most of the upper breast extending from the nipple to the posterior breast tissue; it measures approximately 7.3 x 14 x 9.1 cm in transverse, anteroposterior, and craniocaudal dimensions, respectively. There is no evidence of left pectoralis muscle involvement. An MRI-directed second look left breast ultrasonography (**FIGURE 5**) is performed, revealing a small irregular mass in the left breast 1 o'clock position, 10 to 11 cm from the nipple (red arrow). This area had not been imaged in the prior ultrasound scan due to its posterior location far from the nipple. Ultrasound-guided core needle biopsy is performed; moderately differentiated invasive ductal carcinoma (IDC) with high-grade DCIS is found.

When to refer for surgery

No surgical evaluation or intervention is needed for physiologic nipple discharge. As mentioned previously, reassure the patient and recommend appropriate breast cancer screening. In the setting of pathologic discharge, however, referral to a breast surgeon may be indicated after appropriate imaging workup has been done.

Since abnormal imaging almost always results in a recommendation for image-guided biopsy, typically the biopsy is performed prior to the surgical consultation. Once the pathology report from the biopsy is available, the radiologist makes a radiologic-pathologic concordance statement and recommends surgical consultation. This process allows the surgeon to have all the necessary information at the initial visit.

However, in the setting of pathologic nipple discharge with normal breast imaging, the surgeon and patient may opt for close observation or surgery for definitive diagnosis. Surgical options include single-duct excision when nipple discharge is localized to one duct or central duct excision when nipple discharge cannot be localized to one duct.

CASE Continued: Follow-up

The patient was referred to a breast surgeon. Given the extent of disease in the left breast, breast conservation was not possible. The patient underwent left breast simple mastectomy with sentinel lymph node biopsy and prophylactic right simple mastectomy. Final pathology results revealed stage IA IDC with DCIS. Sentinel lymph nodes were negative for malignancy. The patient underwent adjuvant left chest wall radiation, endocrine therapy with tamoxifen, and implant reconstruction. After 2 years of follow-up, she is disease free.

In summary

Nipple discharge can be classified as physiologic or pathologic. For pathologic discharge, a thorough physical examination should be performed with subsequent imaging evaluation. First-line tools, based on patient age, include diagnostic mammography and targeted ultrasonography. Contrast-enhanced MRI is then recommended for negative or equivocal cases. All patients with pathologic nipple discharge should be referred to a breast surgeon following appropriate imaging evaluation. ●

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Progesterone for preterm delivery prevention

Three cases explore the questions of yay or nay and appropriate administration routes

Alex C. Vidaeff, MD, MPH

IN THIS ARTICLE

Researchers have been studying the use of exogenous progestins for prevention of preterm delivery (PTD) for almost 60 years, but conflicting results contribute to an ongoing debate. Interpretation of the available data is particularly difficult because different forms and doses of progestins have been used in disparate study populations.

Based on available data, progesterone supplementation is not effective as a primary prevention strategy for PTD in the general low-risk obstetric population. PTD is a complex problem with varied and incompletely elucidated pathogenic pathways, making it unlikely that one interventional approach would be effective for all pregnant women. As a result, emerging indications for the use of progesterone are based on risk factors for PTD (ie, prior PTD and/or short cervix). However, this secondary prevention approach is a limiting factor in itself because 50% of women destined to have a PTD have no identifiable risk factors.[1] In addition, researchers have found that progestins are ineffective at delaying delivery for women with multiple gestation, suggesting that a distinct underlying mechanism of early parturition is present in these women, and that this mechanism is unresponsive to progestins.[2]

The formulations used in the study of progestin supplementation for PTD prevention have been almost exclusively either the synthetic 17 alpha-hydroxyprogesterone caproate (17-OHPC) or natural progesterone administered orally or vaginally. In 2003, the American College of Obstetricians and Gynecologists (ACOG) supported the use of progesterone to reduce the rate of PTD,[3] and in 2011, the US Food and Drug Administration (FDA) approved 17-OHPC for use as prophylaxis against recurrent PTD. As a result, in recent years, the perceived standard of care for a majority of practitioners in the United States had been that all women with a previous preterm birth should be offered 17-OHPC. It may be interesting to note that in other parts of the world, the same enthusiastic adoption did not occur. For example, in Australia and New Zealand in 2007, only 5% of practitioners were using progesterone for this indication.[4] Further, 17-OHPC is not recommended by professional guidelines in the United Kingdom and has remained unavailable in Germany.

The publication in 2019 of the PROLONG trial called into question the use of 17-OHPC for the prevention of PTD.[5] In the December 2019 issue of *OBG Management* ("Managing preterm birth in those at risk: Expert strategies"), I expressed the opinion that with

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only rare exceptions, 17-OHPC is no longer a viable option for recurrent PTD prevention.[6] In light of these developments, what scientific evidence is relevant and applicable to the care of women at risk for PTD?

CASE 1 Previous spontaneous PTD at 31 weeks

MC is an asymptomatic 32-year-old woman with a singleton pregnancy at 13 weeks' gestation. You see her for a maternal-fetal medicine consultation because 2 years ago she had a spontaneous PTD at 31 weeks' gestation. What management recommendations can you make to decrease her risk of recurrent PTD?

Cervical length measurement narrows in on risk

The indication "previous preterm birth" is largely meaningless because of the heterogeneity in preterm birth pathways (preterm birth as a syndrome[7]) and inadequate risk characterization. Among women who experience a spontaneous PTD, 70% to 80% do not deliver prematurely in subsequent pregnancies.[8] To better characterize the risk of PTD recurrence, ultrasound assessment of cervical length should be used. Research has shown that among women with a prior spontaneous PTD who maintain a normal cervical length until 24 weeks' gestation, more than 90% will deliver at 35 weeks or after without intervention.[9] Such an approach not only identifies the subgroup of women at significantly increased risk of recurrence but also eliminates unnecessary interventions.

Cervical ultrasound surveillance should be initiated at 16 weeks' gestation. A short cervix before 16 weeks is not associated with a statistically significant increase in risk for PTD.[10] Shortening of the cervix begins approximately 10 weeks before delivery in any gestational age group.[11] Therefore, ultrasound assessment of the cervix at 28 weeks and after is irrelevant. In addition, after 28 weeks, cervical length varies greatly leading to loss in the predictive power of the cervical measurement.[12] Based on these considerations, cervical surveillance may be extended up to 26 weeks. Although cervical cerclage is not an option in the United States in cases in which a short cervix is detected between 24 and 26 weeks, vaginal progesterone supplementation may still be considered.

CASE 1 Continued

MC was started on ultrasound cervical surveillance at 16 weeks' gestation. Her cervical length was initially normal (> 2.5 cm), but at 18 weeks the measurement was 2.2 cm. What is your recommendation?

The value of vaginal progesterone

There appears to be increasing consensus on the value of vaginal progesterone for women with a midtrimester short cervix on sonography, with or without a history of PTD. An individual patient data meta-analysis demonstrated the benefits of vaginal progesterone.[13] Although there was no evidence of an effect on PTD at less than 37 weeks, the rates of PTD at less than 36 weeks and spontaneous PTD at less than 34 weeks were significantly reduced (by 20% and 28%, respectively). Also, there was a significant reduction in the risk of respiratory distress syndrome (53%) and composite neonatal morbidity and mortality (41%), with no significant impact on infant development up to the second year of life.[13]

The lack of generalizable evidence of benefit on childhood outcomes, combined with considerable uncertainty about the exact role and mechanism of action of exogenous progestins, contribute to the ongoing debate. Vaginal progesterone dosage regimens have been based on extrapolations from experience with progesterone in nonpregnant women, and recent pharmacokinetic studies have revealed how precarious such extrapolations may be. As an example, in nonpregnant women, the bioavailability of oral and vaginal progesterone is similar.[14] In pregnancy, however, while daily oral progesterone doubles a pregnant woman's serum progesterone level,[15] daily vaginal administration of progesterone results in only a modest rise in serum

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Most (90%) of women with prior PTD who maintain a normal cervical length until 24 weeks will deliver at or after 35 weeks' gestation without intervention

progesterone, with a coefficient of variation among individuals that is double that outside of pregnancy.[16] It is, therefore, considered that vaginal progesterone in pregnancy may have a local action secondary to the uterine first-pass effect. The uterine first-pass effect for vaginal progesterone was described in nonpregnant women and is only assumed to occur in pregnancy as well.[17]

After evaluating the data from the largest available study of vaginal progesterone,[18] the FDA concluded in 2012 that the study did not meet the statistical significance generally expected to support the approval of a new product. However, according to a more comprehensive evidence review developed in 2019 by the National Guideline Alliance in the United Kingdom, women with a history of PTD and women with a short cervix derive an important benefit from the use of vaginal progesterone; thus, this intervention should be offered to them.[19] At this time, a short cervix and PTD prevention are not considered FDA-approved indications for progesterone supplementation in pregnancy. However, vaginal progesterone is FDA approved for use in pregnant women with a history of infertility.

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Limited observational data seem to suggest that vaginal progesterone plus cerclage have added benefit

CASE 1 Continued

MC initiated treatment with daily vaginal progesterone at 18 weeks' gestation and returned for ultrasound cervical length examination weekly instead of every other week. At 20 weeks' gestation, cervical length was 2.0 cm; the following week it was 1.4 cm. What would you recommend at this point?

When to consider cerclage

If cervical shortening progresses to about 1.5 cm while a woman is being treated with vaginal progesterone, cerclage may be considered. The benefit of cerclage in patients with prior PTD and a short cervix was highlighted in a 2018 Cochrane Review.[20] In this stepwise management approach to a short cervix, waiting for a cervix to be less than 1.5 cm may be unadvisable. Under conditions of a very short cervix that is frequently dilated with exposure of fetal membranes, ascending subclinical intra-amniotic infection may already be present, reducing the efficacy of any preventive measures. Preferential consideration for cerclage from the start over initial vaginal progesterone also may be appropriate when there is a history of 2 spontaneous PTDs or mid-trimester losses, a history of a successful cerclage, or with a very short cervix (< 1.0 cm) at the initial evaluation. As for the latter, a 2018 individual patient data meta-analysis of vaginal progesterone found no benefit when the cervix was less than 1.0 cm.[13]

Progesterone plus cerclage likely to add benefit

The results of an adjusted indirect comparison meta-analysis suggest that both interventions—vaginal progesterone and cerclage—are equally effective.[21] Assuming that there is no clinically meaningful difference in benefit associated with these 2 treatments, the next logical question is whether combining the 2 therapies provides any added benefit; limited observational data seem to suggest that it does. In a retrospective cohort of 86 consecutive singleton pregnancies among women who underwent ultrasound-indicated cerclage, those who used vaginal progesterone after cerclage (n = 45) had a lower rate of PTD.[22] Also, a small (66 cases) case-control study demonstrated the benefit of administration of vaginal progesterone as a rescue intervention in women with cerclage and progressive cervical shortening despite cerclage.[23]

CASE 2 Woman experiences adverse effects from vaginal progesterone

MS is a 25-year-old G2P0101 who was started on vaginal progesterone as prophylaxis for recurrent PTD. She is now at 20 weeks' gestation, with a stable remnant cervical length of 2.0 cm. She is reporting an increasing vaginal burning sensation and vaginal discharge caused by the nightly vaginal progesterone applications, to the point that she is unwilling to continue the treatment. She asks if any alternatives to vaginal progesterone are available to decrease her risk of PTD.

Is oral progesterone an option?

In the 1980s and 1990s, oral micronized progesterone was widely used in France at doses of 900 to 1,200 mg/d for women at risk for PTD. The practice was stopped when secondary hepatic effects, including cholestasis of pregnancy, were reported at a higher rate in treated women.[24] A rise in the serum concentration of progesterone metabolites has been associated with impaired biliary excretion and subsequent accumulation of bile acids.[25] In other reports, elevated serum transaminase activity was found in pregnant women treated with oral micronized progesterone, and withdrawal of treatment frequently has led to improvement in transaminase levels.[26] The synthesis of endogenous progesterone during normal pregnancy is between 250 and 500 mg/d,[26] and experts have expressed concern that exogenous progesterone supplementation may impose an additional load on the hepatic transport of sulfated metabolites. Unlike orally administered progesterone, progestins given by the vaginal route avoid the hepatic first-pass effect. For this reason, they may be associated with less hepatic dysfunction.

Although not recommended by professional guidelines, oral progesterone administration for the prevention of PTD has been used in the United States. A 2015 survey of Wisconsin prenatal care providers found that of those who prescribed any progesterone for PTD prevention, oral progesterone was prescribed by 13.1% of obstetricians, 24.4% of midwives, and 40.7% of family medicine practitioners.[27]

Some limited recent evidence from a meta-analysis of 3 trials investigating oral progesterone versus placebo suggests effectiveness in the prevention of recurrent PTD and reduction in perinatal morbidity and mortality.[15] However, the number of cases included in the meta-analysis (386) was too small to support definitive clinical recommendations. Furthermore, questions have been raised in the literature about the reliability of the largest trial included in that meta-analysis.[28]

CASE 3 Two previous spontaneous PTDs

A 29-year-old G3P0201 presents for her first prenatal appointment at 10 weeks' gestation. With her first pregnancy she had a spontaneous PTD at 23 weeks, and the neonate did not survive. In her second pregnancy, she was treated with 17-OHPC from 16 weeks' gestation. She had a spontaneous PTD at 29 weeks, and that child is developing normally by her report. She believes that 17-OHPC helped her in her last pregnancy and is anxious about the risk for still another PTD. Consistent with the concept of shared decision-making, you inform her of the results of the recent PROLONG trial and statements on the subject released by professional organizations such as ACOG and the Society for Maternal-Fetal Medicine (SMFM). What options does she have?

17-OHPC may be a possibility in very high-risk women

According to a SMFM statement released in the wake of the PROLONG trial publication, ". . . SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial".[29] Only a few women will have a recurrence risk of PTD over 50%, as was the background event rate in the Meis trial.[30] Such a risk level may be suspected, as an example, in women with 2 or more prior early (before 34 weeks) PTDs without intervening term deliveries. Even in those cases, if treatment with 17-OHPC is decided upon, ultrasound cervical surveillance should be added as an additional safety measure. ●

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Progestins given by the vaginal route avoid the hepatic first-pass effect and may be associated with less hepatic dysfunction than orally administered progesterone

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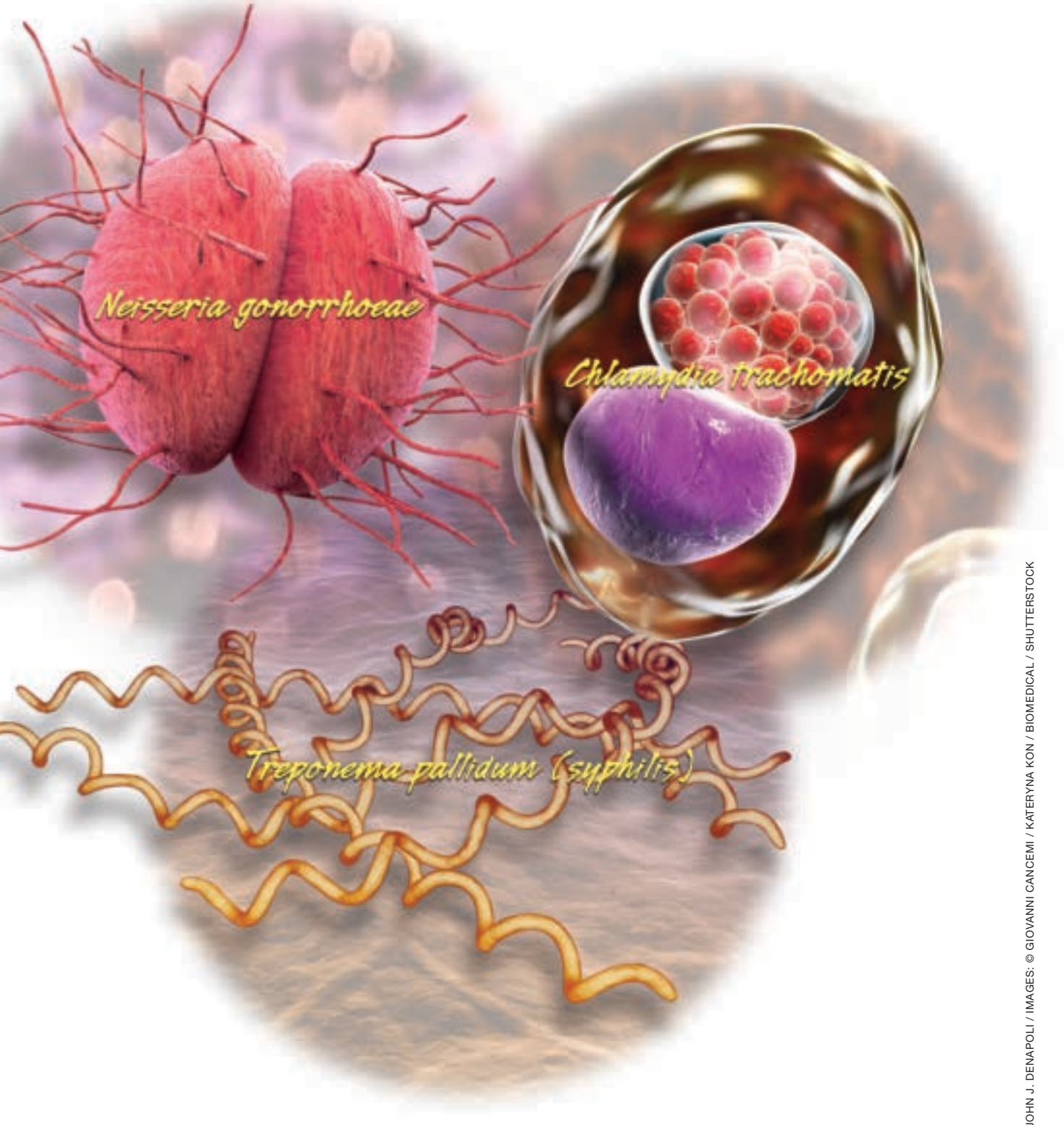

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The STD epidemic: Why we need to care about this escalating problem

Sexually transmitted diseases have broad-reaching impact on women's health and maternal-child health. ObGyn engagement in evidence-based strategies and population-based health initiatives can help de-escalate the ongoing spread of these infections.

Lisa B. Haddad, MD, MS, MPH, and Melissa J. Kottke, MD, MPH, MBA

The sexually transmitted disease (STD) epidemic in the United States is intensifying, and it disproportionately impacts high-risk communities. In 2018, rates of reportable STDs, including syphilis and *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections, reached an all-time high.[1] That year, there were 1.8 million cases of chlamydia (increased 19% since 2014), 583,405 cases of gonorrhea (increased 63% since 2014), and 35,063 cases of primary and secondary syphilis (71% increase from 2014).[1]

Cases of newborn syphilis have more than doubled in 4 years, with rates reaching a 20-year high.[1]

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This surge has not received the attention it deserves given the broad-reaching impact of these infections on women's health and maternal-child health.[2] As ObGyns, we are on the front line, and we need to be engaged in evidence-based strategies and population-based health initiatives to expedite diagnoses and treatment and to reduce the ongoing spread of these infections.

Disparities exist and continue to fuel this epidemic

The STD burden is disproportionately high among reproductive-aged women, and half of all reported STDs occur in women aged 15 to 24 years. African American women have rates up to 12 times higher than white women.[3,4] Substantial geographic variability also exists, with the South, Southeast, and West having some of the highest STD rates.

These disparities are fueled by inequalities in socioeconomic status (SES), including employment, insurance, education, incarceration, stress/trauma exposure, and discrimination.[5-7] Those with lower SES often have trouble accessing and affording quality health care, including sexual health services. Access to quality health care, including STD prevention and treatment, that meets the needs of

IN THIS ARTICLE

lower SES populations is key to reducing STD disparities in the United States; however, access likely will be insufficient unless the structural inequities that drive these disparities are addressed.

Clinical consequences for women, infants, and mothers

STDs are most prevalent among reproductive-aged women and can lead to pelvic inflammatory disease, infertility, ectopic pregnancy,[4,8] and increased risk of acquiring human immunodeficiency virus (HIV). STDs during pregnancy present additional consequences. Congenital syphilis is perhaps the most salient, with neonates experiencing substantial disability or death.

In addition, STDs contribute to overall peripartum and long-term adverse health outcomes.[4,9,10] Untreated chlamydia infection, for example, is associated with neonatal pneumonia, neonatal conjunctivitis, low birth weight, premature rupture of membranes, preterm labor, and postpartum endometritis.[2,11] Untreated gonorrhea is linked to disseminated gonococcal infection in the newborn, neonatal conjunctivitis, low birth weight, miscarriage, premature rupture of membranes, preterm labor, and chorioamnionitis.[2,12]

As preterm birth is the leading cause of infant morbidity and mortality and disproportionately affects African American women and women in the southeastern United States,[13] there is a critical public heath need to improve STD screening, treatment, and prevention of reinfection among high-risk pregnant women.

Quality clinical services for STDs: Areas for focus

More and more, STDs are being diagnosed in primary care settings. In January 2020, the Centers for Disease Control and Prevention (CDC) released a document, referred to as STD QCS (quality clinical services), that outlines recommendations for basic and specialty-level STD clinical services.[14] ObGyns and other clinicians who provide primary care should meet the basic recommendations as a minimum.

FAST TRACK

The STD QCS document outlines 8 recommendations for basic and specialty-level STD clinical services. ObGyns and other primary care clinicians should, as a minimum, meet the basic recommendations.

The STD QCS outlines 8 recommendation areas: sexual history and physical examination, prevention, screening, partner services, evaluation of STD-related conditions, laboratory, treatment, and referral to a specialist for complex STD or STD-related conditions.[14] These recommendations can be used by providers, managers, advocates, and others working to implement the highest-quality STD clinical services. Below are key areas that can be addressed in ObGyn practice.

Sexual history and physical examination

A complete sexual history and risk assessment should be performed at a complete initial or annual visit and as indicated. Routinely updating the sexual history and risk assessment is important to normalize these questions within the frame of the person's overall health, and it may be valuable in reducing stigma. This routine approach may be important particularly for younger patients and others whose risk for STDs may change frequently and dramatically.

Creating a safe space that permits privacy and assurance of confidentiality may help build trust and set the stage for disclosure. The American College of Obstetricians and Gynecologists recommends that all young people have time alone without parents for confidential counseling and discussion.[15] All states allow minors to consent for STD services themselves, although 11 states limit this to those beyond a certain age.[16]

The CDC recommends using the 5 P's—partners, practices, protection, past history of STDs, and prevention of pregnancy—as a guide for discussion.[14] ObGyns are more likely than other providers to perform this screening routinely. While a pelvic examination should be available for STD evaluation as needed, it is not required for routine screening.

Prevention

ObGyns should employ several recommendations for STD prevention. These include providing or referring patients for vaccination against hepatitis B and human

papillomavirus and providing brief STD/HIV prevention counseling along with contraceptive counseling. ObGyns should be familiar with HIV pre-exposure prophylaxis (PrEP) and nonoccupational postexposure prophylaxis (nPEP) and provide risk assessment, education, and referral or link to HIV care. Providing these services would improve access to care and further remove barriers to care. ObGyns also could consider providing condoms in their offices.[14]

Screening

STD screening of women at risk is critical since more than 80% of infected women are asymptomatic.[8] Because young people are disproportionately experiencing STDs, annual screening for chlamydia and gonorrhea is recommended for women younger than 25 years. For women older than 25, those at increased risk can be screened.

Risk factors for chlamydia infection include having new or multiple sex partners, sex partners with concurrent partners, or sex partners who have an STD. For gonorrhea, risk factors include living in a high-morbidity area, having a previous or coexisting STD, new or multiple sex partners, inconsistent condom use in people who are not in a mutually monogamous relationship, and exchanging sex for money or drugs. Screening for syphilis in nonpregnant women is recommended for those who have had any sexual activity with a person recently diagnosed with syphilis or those who personally display signs or symptoms of infection.[17]

STD screening is especially important for pregnant women, and treatment of infections may improve pregnancy outcomes. The CDC recommends screening at the first prenatal care visit for chlamydia and gonorrhea in pregnant women younger than 25 years of age and in older pregnant women at increased risk; women younger than 25 years or at continued high risk should be rescreened in their third trimester. The CDC recommends screening all women for syphilis at their first prenatal care visit and rescreening those at high risk in the third trimester and at delivery (**TABLE,** page 42).[18]

Recommendations for ObGyn providers

- Be aware of up-to-date screening, treatment, and follow-up recommendations for STDs
- Develop strategies to maximize partner treatment, including expedited partner therapy
- Identify high-risk individuals for whom counseling on HIV and unintended pregnancy prevention strategies can be reinforced, including PrEP and contraception
- Create a clinical environment that normalizes STD testing and destigmatizes infection
- Integrate client-centered counseling to improve protective health behaviors

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; STD, sexually transmitted disease.

Partner services

Clearly outlined partner management services is paramount for preventing STD reinfection.[14] Reinfection rates for chlamydia and gonorrhea among young women are high and vary by study population.[19] At a minimum, ObGyns should counsel patients with an STD that their partner(s) should be notified and encouraged to seek services.

For states in which it is legal, expedited partner therapy (EPT)—the clinician provides medication for the partner without seeing the partner—should be provided for chlamydia or gonorrhea if the partner is unlikely to access timely care. EPT is legal in most states. (To check the legal status of EPT in your state, visit https://www.cdc.gov/std/ept/legal/default.htm.) Research is needed to evaluate optimal strategies for effective implementation of EPT services in different clinical settings.

Laboratory tests

ObGyns should be able to provide a wide range of laboratory evaluations (for example, a nucleic acid amplification test [NAAT] for genital chlamydia and gonorrhea, quantitative nontreponemal serologic test for syphilis, treponemal serologic test for syphilis) that can be ordered for screening or diagnostic purposes. To improve rates of recommended screening, consider having clinic-level policies that support screening, such as standing

FAST TRACK

Young people are disproportionately experiencing STDs. Thus, annual screening for chlamydia and gonorrhea is recommended for women < 25 years. For women older than 25, those at increased risk can be screened.

TABLE CDC guidelines for STD screening, treatment, and test of reinfection[8]

	Screening non-pregnant women	Screening in pregnancy	Screening for women living with HIV	Treatment	Test of reinfection
Chlamydia	Annual screening of all sexually active women aged < 25 years and older women at increased risk for infection	• < 25 years of age at first PNC visit • ≥ 25 years of age and high risk[a] at first PNC visit • Rescreen those < 25 years of age or at continued high risk[a] in third trimester	• At initial HIV care visit • At least annually after initial care visit	Single dose oral azithromycin 1 g	• Repeat at 3 months after treatment completion • In pregnancy, repeat 3-4 weeks after treatment completion for chlamydia to ensure adequate treatment
Gonorrhea				Single dose IM ceftriaxone 250 mg plus single dose oral azithromycin 1 g	
Syphilis	Annual test for persons with increased risk	• A serologic test for syphilis should be performed for all pregnant women at first PNC visit • High-risk women[a]: rescreen in third trimester and at delivery		Parenteral penicillin G (preparation, dosage, and length of treatment depend on stage and clinical manifestations of disease)	6 and 12 months after treatment

[a]For chlamydia: New/multiple sex partners, sex partners with concurrent partners, sex partners who have STDs.

For gonorrhea: Live in a high-morbidity area, previous/coexisting STD, new/multiple sex partners, unprotected sex in nonmonogamous relationships, exchange sex for money/drugs.

For syphilis: Any person who has signs or symptoms suggestive of syphilis or anyone with an oral, anal, or vaginal sex partner who recently has been diagnosed with syphilis.

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IM, intramuscularly; PNC, prenatal care; STD, sexually transmitted disease.

orders, express or walk-in screening appointments, lab panels, and reflex testing.

Further, having rapid results or point-of-care testing available would help decrease lags in time to treatment. Delays in treatment are particularly important in lower-resource communities; thus, point-of-care testing may be especially valuable with immediate access to treatment on site.

Treatment

Adequate and timely treatment of STDs is critical to decrease sequelae and the likelihood of transmission to others. Treatment is evolving, particularly for gonorrhea. Over the past several years, gonorrhea has become resistant to 6 previously recommended treatment options.[20] Since 2015, the CDC recommends dual therapy for gonorrhea with an injection of ceftriaxone and oral azithromycin.

The first-line recommended treatments for bacterial STDs are listed in the TABLE. When possible, it is preferred to offer directly observed therapy at the time of the visit. This decreases the time to treatment and ensures that therapy is completed.

A call to action for ObGyns

Clinicians have multiple opportunities to address and reduce the surge of STDs in the United States. We play a critical role in screening, diagnosing, and treating patients, and it is thus imperative to be up-to-date on the recommended guidelines. Further, clinicians can advocate for more rapid

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testing modalities, with the goal of obtaining point-of-care testing results when possible and implementing strategies to improve partner treatment.

While a positive STD result may be associated with significant patient distress, it also may be an opportunity for enhancing the patient-provider relationship, coupling education with motivational approaches to help patients increase protective health behaviors.

It is critical to approach clinical care in a nonjudgmental manner to improve patients' comfort in their relationship with the health care system. ●

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***Chlamydia trachomatis* infections**

Aalekhya Tenali, BS, BA, and Patrick Duff, MD Find it at mdedge.com/obgyn

COVID-19 during pregnancy: How would you proceed in this case of a novel and ominous emerging pathogen?

Patrick Duff, MD See page 45

COVID-19 during pregnancy: How would you proceed in this case of a novel and ominous emerging pathogen?

Your patient has just traveled from Italy. She has a fever, and she is 12 weeks' gestation. What are the most likely diagnoses? What diagnostic tests and clinical treatments are indicated?

Patrick Duff, MD

CASE Pregnant patient with fever who has travel history to Italy

A 28-year-old primigravid woman at 12 weeks' gestation just returned from a 2-week vacation in Italy. She requests medical evaluation because of malaise; fever; chills; rhinorrhea; mild dyspnea; a dry, nonproductive cough; and diarrhea. On physical examination, her temperature is 38.6° C (101.5° F), pulse 104 bpm, respirations 22/minute, and blood pressure 100/70 mm Hg. Auscultation of the lungs demonstrates scattered rales, rhonchi, and expiratory wheezes in both posterior lung fields. The fetal heart rate is 168 bpm.

What are the most likely diagnoses? What diagnostic tests are indicated? And what clinical treatment is indicated?

In the presented case scenario, the patient's symptoms are consistent with a viral influenza. Her recent travel history certainly makes coronavirus disease 2019 (COVID-19) the most likely diagnosis.

COVID-19, caused by a novel new coronavirus, has evolved with lightning speed since it was identified in early December 2019.[1] The disease originated in Wuhan, China. Its epicenter is now in Europe, and over 100 countries and regions have reported cases. New US cases are being identified daily, and there is no clear end to the outbreak. Several areas of the United States have been particularly hard hit by this disease, including Seattle, New Orleans, and New York.

IN THIS ARTICLE

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This article was published online first March 19, 2020. It was updated on April 2, 2020. Information regarding COVID-19 is being generated rapidly. New evidence may supersede the insights and guidance provided in this article.

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TABLE Unanswered questions about COVID-19

- Does the risk of transmission vary with the severity of illness in the affected patient, and how important are asymptomatic persons as vectors for spread of the disease?
- How important are environmental surfaces in facilitating transmission of the virus?
- How long can organisms remain viable on environmental surfaces?
- How long is the pandemic likely to persist?
- How soon will a vaccine be available? Will it still prove effective if the virus mutates significantly in future years?
- How quickly will effective antiviral agents be available?
- Following natural infection, will immunity be sustained and lifelong?
- Will perinatal transmission eventually be documented? Will its frequency vary in accordance with the trimester in which maternal infection occurs?
- Will pregnant women ultimately be shown to be more susceptible to COVID-19 and more likely to develop serious complications?

FAST TRACK

COVID-19 is transmitted directly by respiratory droplets and by close surface-to-hand contact with respiratory secretions

COVID-19 has provoked widespread unsettledness in many populations and an extraordinary response from public health officials, large corporations, professional organizations, and financial markets. We are learning more about somewhat unfamiliar public health concepts such as quarantine, containment, mitigation, reproduction number (R), and "flattening the curve." Disneyland and Walt Disney World are temporarily closed. Professional and collegiate sports organizations have cancelled or suspended games and tournaments. Scientific and trade association meetings have been postponed or cancelled. Broadway, Carnegie Hall, and the Metropolitan Museum of Art have "turned out the lights." The Centers for Disease Control and Prevention has recommended that everyone avoid gatherings that include more than 10 other persons.

This article will review the evolving epidemiology of COVID-19, describe the usual clinical manifestations of the disease, highlight the key diagnostic tests, and present guidelines for treatment. It will review the limited information currently available about the impact of COVID-19 in pregnant women. The review will conclude by describing measures that individuals can employ to prevent acquisition or transmission of infection and then by highlighting key "unanswered questions" about this new and ominous pathogen (**TABLE**).

What we know about epidemiology

COVID-19 is caused by a novel new coronavirus that shares some genetic overlap with the viruses that caused Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[2] The first case of COVID-19 was reported on December 1, 2019, from Wuhan, China.[1] Within a very short period of time the disease has spread throughout the world, and on March 11, 2020, the World Health Organization (WHO) declared the infection to be a true pandemic. The countries with the highest prevalence of COVID-19 include China, South Korea, Iran, Italy, France, Spain, and the United States. However, more than 100 other countries and regions have reported cases. As of the first week of April, approximately 1 million persons in the world have been diagnosed with COVID-19. Of those infected, about 50,000 deaths have occurred. At the time of this writing, 234,483 cases have been documented in the United States, with deaths in more than 5,000 patients. Current estimates indicate that approximately 7% of the population in the country could become infected.[1,3,4]

The virus responsible for COVID-19 is a single-stranded, enveloped RNA virus. Like its counterparts that caused SARS and MERS, this virus originates in animals, primarily bats. The early cases seem to have resulted from patient contact with exotic animals displayed in the Huanan Seafood Wholesale Market.[1]

The virus is transmitted directly by respiratory droplets and by close surface-to-hand contact with infected respiratory secretions. The virus appears to remain viable on environmental surfaces for 1 to 3 days, although the degree of infectivity over time is not well delineated. With direct exposure to respiratory droplets, the infectivity is relatively high; approximately 2 to 3 individuals become infected as the result of contact with an infected patient. By contrast,

the "reproduction number (R)" for influenza is closer to 1.[2,5]

Certain persons appear to be at increased risk for developing infection and becoming seriously ill[2,6]:

- persons older than age 60
- persons with underlying medical illness
- persons who are immunosuppressed.

The reported range in the case fatality rate (CFR) varies from 1% to 13%, with the higher rates concentrated in older patients with comorbidities.[3] These initial reports of high CFRs may be misleading because in the initial phases of this pandemic many patients with mild or no symptoms were not tested, and, thus, the overall prevalence of infection is not clear. By way of comparison, the CRF for influenza A and B is about 0.1%.[2]

Of note, the number of reported cases in the pediatric population is low, and the outcomes in these individuals are much better than in the older population.[2,3,6] At present, there are only two reports of COVID-19 in pregnancy; these two studies include 18 women and 19 infants.[7,8] The frequency of preterm delivery was 50% in these reports. Sixteen of the 18 patients were delivered by cesarean delivery; at least 6 of these procedures were performed for a non-reassuring fetal heart rate tracing. No maternal deaths were identified, and no cases of vertical transmission occurred.

We must remember that the number of patients described in these two reports is very small. Although the initial reports are favorable, in other influenza epidemics, pregnant women have not fared so well and have experienced disproportionately higher rates of morbidity and mortality.[2]

Reported clinical manifestations

The incubation period of COVID-19 ranges from 2 to 14 days; the median is 5.2 days. Many patients with proven COVID-19 infection are asymptomatic. When clinical findings are present, they usually are relatively mild and include lowgrade fever, myalgias, arthralgias, sore throat, mild dyspnea, and a dry, nonproductive cough. Some patients also may experience diarrhea. Of course, these findings are also consistent with influenza A or B or atypical pneumonia. One key to differentiation is the patient's history of recent travel to an area of high COVID-19 prevalence or contact with a person who has been in one of these areas and who is clinically ill.[2,3,9,10]

In some patients, notably those who are older than 65 years of age and/or who have underlying medical illnesses, the respiratory manifestations are more prominent.[6] These patients may develop severe dyspnea, pneumonia, adult respiratory distress syndrome (ARDS), multiorgan failure, and septic shock. Interestingly, the more severe manifestations tend to occur during the second week of the illness. In this group of more severely ill patients requiring hospitalization, 17% to 29% develop ARDS, and 23% to 32% require admission to the intensive care unit.[2,6]

Pregnant patients who become severely ill may be at risk for spontaneous miscarriage and preterm labor. With profound maternal hypoxia, fetal heart rate abnormalities may become apparent. To date, no clearly proven cases of vertical transmission of infection to the newborn have been identified. However, as noted above, current reports only include 18 pregnancies and 19 infants.[2,3,7,8,11]

Diagnostic testing

Infected patients may have a decreased peripheral white blood cell count, with a specific decrease in the number of lymphocytes. Thrombocytopenia may be present, as well as an elevation in the hepatic transaminase enzymes (ALT, AST).[2]

X-ray, chest CT, and RT-PCR. The three most important diagnostic tests are chest x-ray, chest computed tomography (CT) scan, and real-time PCR (RT-PCR) or nucleic acid amplification test (NAAT).[2,6] Specimens for RT-PCR or NAAT should be obtained from the oropharynx and nasopharynx using a synthetic-tipped applicator with an aluminum shaft. Patients who are intubated should have specimens obtained by bronchoalveolar lavage. The virus also has been recovered

FAST TRACK

With limited reports available, no clearly proven cases of vertical transmission of infection from mother to newborn have been identified

from blood and stool, but not yet from urine, amniotic fluid, placenta, cord blood, or breast milk.[2]

CT and chest x-ray show characteristic groundglass opacities in both lung fields, combined with multiple areas of consolidation. Chest imaging is particularly helpful when the patient has all the major clinical manifestations, but the initial RT-PCR or NAAT is negative.

Treatment

Fortunately, most infected persons can be treated as outpatients. Because this condition may be confused with influenza A or B, initial treatment with a drug such as oseltamivir 75 mg orally twice daily for five days is very reasonable.[9] Supportive therapy is critically important in this clinical setting. Acetaminophen, up to 3,000 mg/d in divided doses, or ibuprofen, up to 2,400 mg/d in divided doses, can be used to reduce fever and relieve myalgias and arthralgias. The latter drug, of course, should not be used in pregnant women. The patient should be encouraged to rest and to stay well hydrated. Loperamide can be used to treat diarrhea, 4 mg orally initially, then 2 mg orally after each loose stool up to a maximum of 16 mg/d. Pregnant patients should be cautioned to watch for signs of preterm labor.[9,12] Patients should remain in relative isolation at home until they are free of signs of illness and they test negative for COVID-19.

FAST TRACK

Pregnant patients should be cautioned to watch for signs of preterm labor

For patients who are more severely ill at initial evaluation or who deteriorate while undergoing outpatient management, hospitalization is indicated.[2,6] Patients should be placed in rooms that provide protection against aerosolized infection. They should receive supplemental oxygen and be observed closely for signs of superimposed bacterial infection. Depending upon the suspected bacterial pathogen, appropriate antibiotics may include ceftriaxone, which targets *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis*; azithromycin, which targets mycoplasmas; and vancomycin, which specifically covers *Staphylococcus aureus*. Health care workers should wear appropriate personal protective equipment when interacting with these patients, including cap, N95 mask, face shield, gloves, gown, and shoe covers. If a woman with COVID-19 has delivered, and the pediatrician permits rooming in, the isolette should be positioned at least 6 feet away from the mother. The mother should use a mechanical breast pump to obtain milk and then have another family member feed the baby until the mother tests negative for the virus. The breast pump needs to be cleaned meticulously after each use. The number of visitors to the mother's room should be strictly limited.[3,9]

At the present time, there is no specific antiviral drug approved by the US Food and Drug Administration for treatment of COVID-19. The National Institutes of Health is currently conducting a trial of remdesivir for affected patients.[13] The drug is also available from the manufacturer outside of this trial on a "compassionate use" basis. Another treatment regimen receiving extensive publicity is the combination of azithromycin plus hydroxychloroquine. Its effectiveness has not been confirmed in a properly designed randomized trial.

Prevention hinges on commonsense precautions

Although vaccine trials are underway, public health authorities estimate that a vaccine will not be commercially available for at least 12 to 18 months. Therefore, independent of "community/organizational" mitigation programs, individuals should observe the following commonsense precautions to minimize their risk of contracting or transmitting COVID-19[2,3,5,14]:

- Eliminate any nonessential travel, particularly by plane or cruise ship.
- Avoid events that draw large crowds, such as concerts, theater performances, movies, and even religious services.
- When out in public, try to maintain a distance of 6 feet from others.
- Remain at home if you feel ill, particularly if you have respiratory symptoms.
- Cough or sneeze into your sleeve rather than your bare hand.
- Avoid handshakes.

- Wash your hands frequently in warm soapy water for at least 20 seconds, particularly after touching environmental surfaces such as counter tops and handrails.
- If you use hand sanitizers, they should have an alcohol content of at least 60%.
- Clean environmental surfaces frequently with a dilute bleach solution.

CASE Resolved

The clinical manifestations displayed by this patient are consistent with viral influenza. The recent travel history to one of the European epicenters makes COVID-19 the most likely diagnosis. The patient should have a chest CT scan and a RT-PCR or NAAT to confirm the diagnosis. If the diagnosis is confirmed, she and her close contacts should be self-quarantined at home for 14 days. She should receive appropriate supportive care with antipyretics, analgesics, and antidiarrhea agents. If she develops signs of serious respiratory compromise, she should be admitted to an isolation room in the hospital for intensive respiratory therapy and close observation for superimposed bacterial pneumonia. ●

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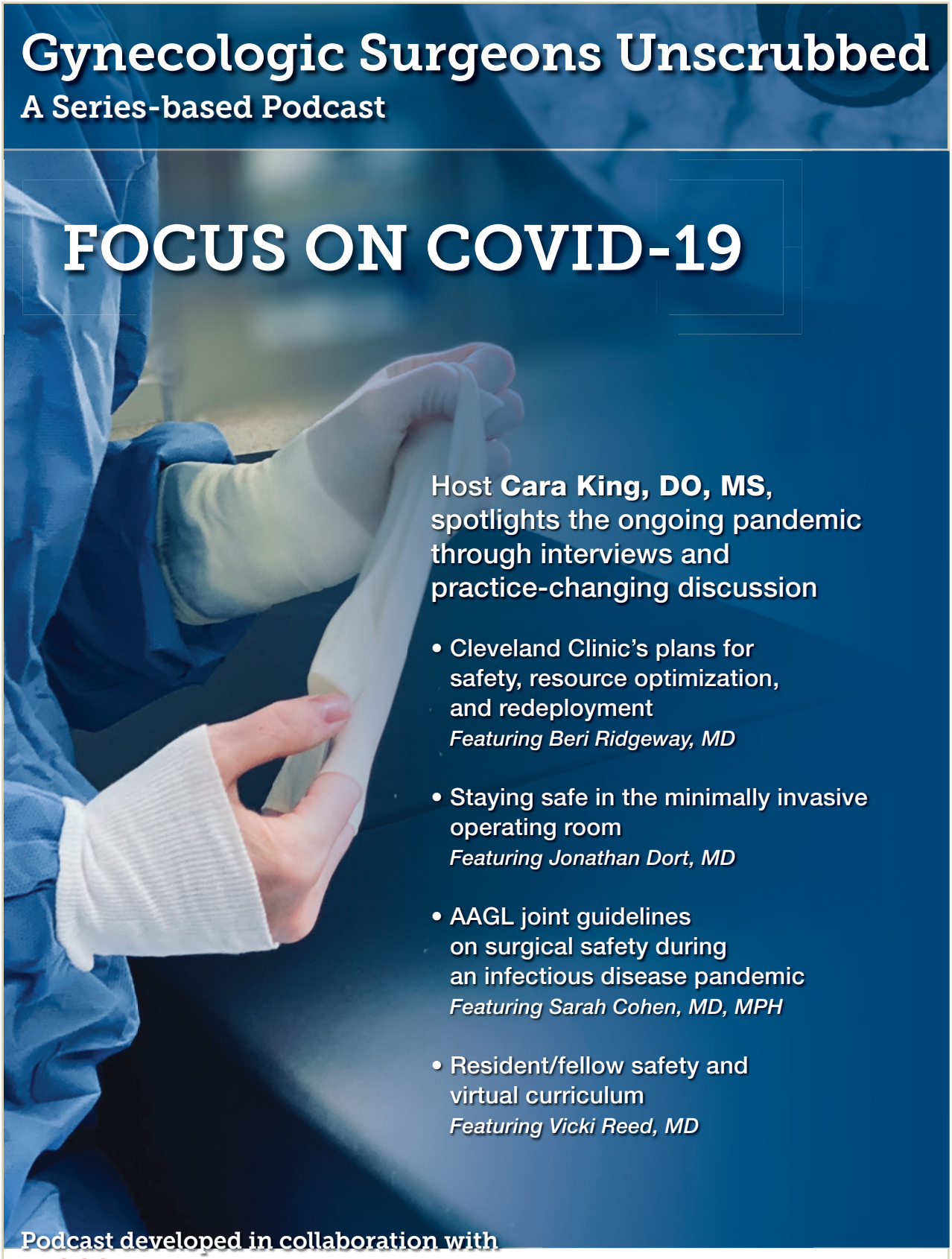

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Reference: 1. R Gomez, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. AJOG 2005; 192: 350-359.

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