MDEDGE.COM/OBGYN | VOL 32, NO 8 | AUGUST 2020

OBG MANAGEMENT

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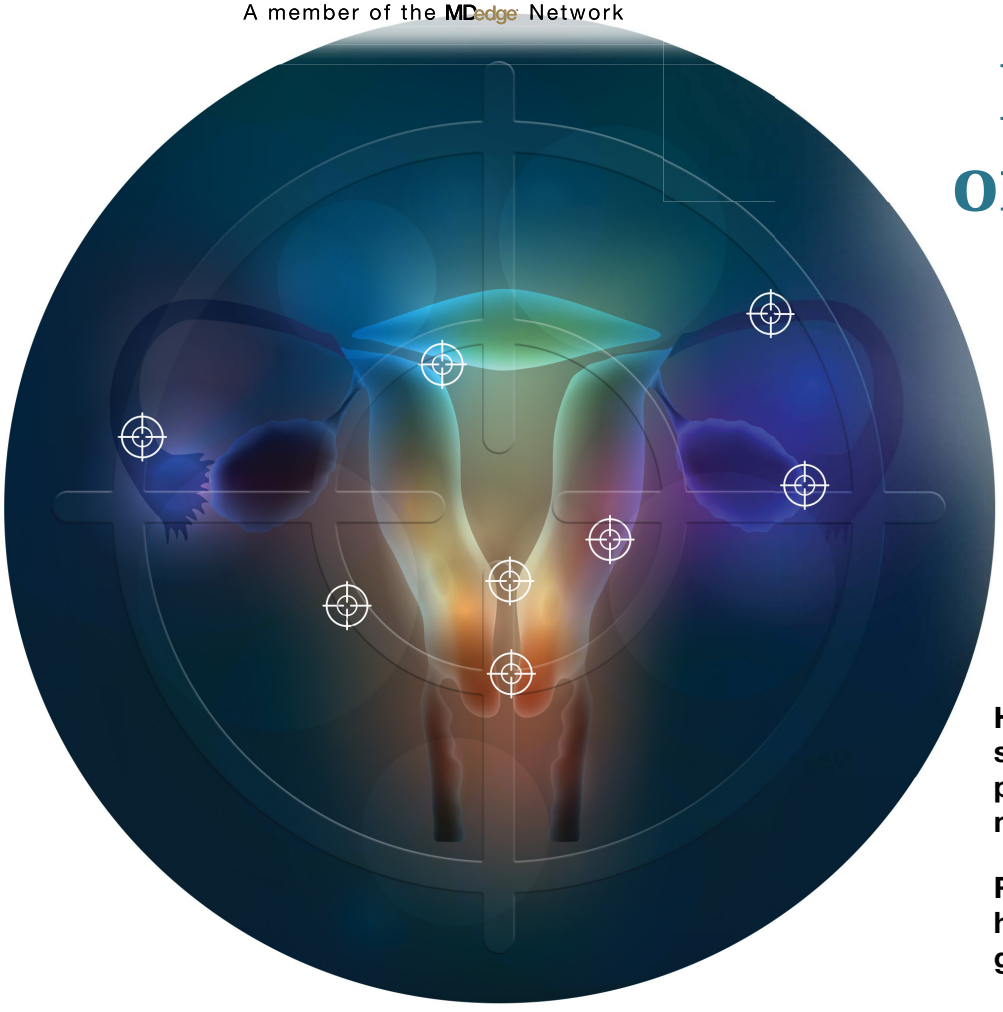
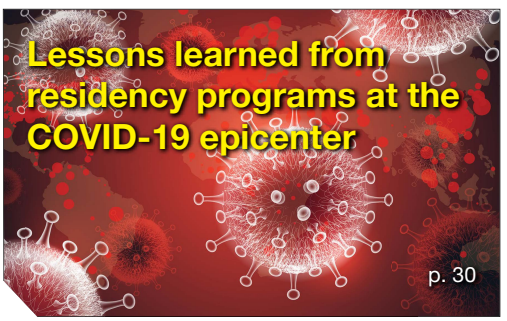


Pregnancy of unknown location

Evaluation and management

Iris G. Insogna, MD,
and Paula C. Brady, MD



pHinally! There's Phexxi™

Birth control designed to meet her contraceptive needs

- **NON-HORMONAL**
- **IN THE MOMENT**
- **WORKS IMMEDIATELY**

AVAILABLE IN PHARMACIES SOON!

Phexxi™ will be available for prescription in the United States in September. For updates on the availability of Phexxi™, and for more information, visit **HCP-Phexxi.com/AvailableSoon**

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

INDICATIONS AND USAGE

Phexxi™ is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

LIMITATIONS OF USE

Phexxi™ is not effective for the prevention of pregnancy when administered after intercourse.

Please see full Prescribing Information for Phexxi™ at HCP-Phexxi.com.

Please see Brief Summary on the following page.

REFERENCE: 1. Phexxi™ [Prescribing Information]. Evofem Biosciences, Inc: San Diego, CA; May 2020.

NOW APPROVED!

phexxi™

(lactic acid, citric acid, and potassium bitartrate) Vaginal Gel 1.8%, 1%, 0.4%

Phexxi™ is a **non-hormonal** contraceptive option that regulates her vaginal pH to prevent pregnancy[1]

AVAILABLE BY PRESCRIPTION

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

Most common adverse reactions were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection, vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain.

Patients should be counseled on the following:

- **To contact and consult with their healthcare provider for severe or prolonged genital irritation or experiencing urinary tract symptoms.**
- **To discontinue Phexxi™ if they develop a local hypersensitivity reaction.**
- **That Phexxi™ does not protect against HIV infection or other sexually transmitted infections.**

phexxi™

(lactic acid, citric acid, and potassium bitartrate) Vaginal Gel 1.8%, 1%, 0.4%

BRIEF SUMMARY: Consult the Package Insert for complete Prescribing Information

INDICATIONS AND USAGE

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

LIMITATIONS OF USE

PHEXXI is not effective for the prevention of pregnancy when administered after intercourse.

WARNINGS AND PRECAUTIONS

Cystitis and Pyelonephritis

Among 2804 subjects who received PHEXXI in Studies 1 and 2, 0.36% (n=10) reported adverse reactions of cystitis, pyelonephritis, or other upper urinary tract infection (UTI). Of these, one case of pyelonephritis was considered serious and required hospitalization. Avoid use of PHEXXI in females of reproductive potential with a history of recurrent urinary tract infection or urinary tract abnormalities.

ADVERSE REACTIONS

Clinical Trials Experience

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

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

Hypersensitivity Reaction:

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

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

Table 1. Adverse Reactions that Occurred in ≥ 2% of Subjects Who Used PHEXXI to Prevent Pregnancy (Studies 1 and 2 – U.S. population only)

Adverse Reaction	PHEXXI (N=2480) (%)
Vulvovaginal Burning Sensation	18.0
Vulvovaginal Pruritus	14.5
Vulvovaginal Mycotic Infection*	9.1
Urinary Tract Infection†,‡	9.0
Vulvovaginal Discomfort	9.0
Bacterial Vaginosis	8.4
Vaginal Discharge	5.5
Genital Discomfort	4.1
Dysuria	3.1
Vulvovaginal pain	2.1

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

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

‡Does not include PTs cystitis, kidney infection, and pyelonephritis [see *Warnings and Precautions (5.1)*].

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

Adverse Reactions in Male Partners:

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Lactation

Risk Summary

There are no data on the presence of lactic acid, citric acid, and potassium bitartrate or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric Use

The safety and effectiveness of PHEXXI have been established in females of reproductive potential.

Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users 17 years and older. The use of PHEXXI before menarche is not indicated.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

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

Advise the patient:

- To intravaginally administer the contents of one pre-filled single-dose applicator of PHEXXI before **each** episode of vaginal intercourse and to administer an additional dose if intercourse does not occur within one hour of administration [*see Dosage and Administration (2.1) of PHEXXI Full Prescribing information*].
- To consult their healthcare provider for severe or prolonged genital irritation [*see Adverse Reactions (6.1) of PHEXXI Full Prescribing information*].
- To discontinue PHEXXI if they develop a local hypersensitivity reaction [*see Adverse Reactions (6.1) of PHEXXI Full Prescribing information*].
- To contact their health care provider if experiencing urinary tract symptoms [*see Warnings and Precautions (5.1) of PHEXXI Full Prescribing information*].
- That PHEXXI does not protect against HIV infection and other sexually transmitted infections.

Manufactured for Evofem, Inc.,
a wholly owned subsidiary of Evofem Biosciences, Inc.,
12400 High Bluff Drive, Suite 600, San Diego, CA 92130

U.S. Patent 6,706,276

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

EVOFEM BIOSCIENCES®

#1 IN READERSHIP*

OBG MANAGEMENT

mdedge.com/obgyn

Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians†

*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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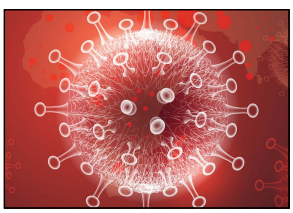
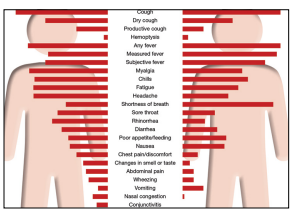
OBG MANAGEMENT



Pandemic playbook **30**



COVID-19 symptoms **C3**

FAST TRACK is a system to enable you as a reader to move quickly through each issue of **OBG MANAGEMENT**, identifying articles or sections of articles to read in depth.

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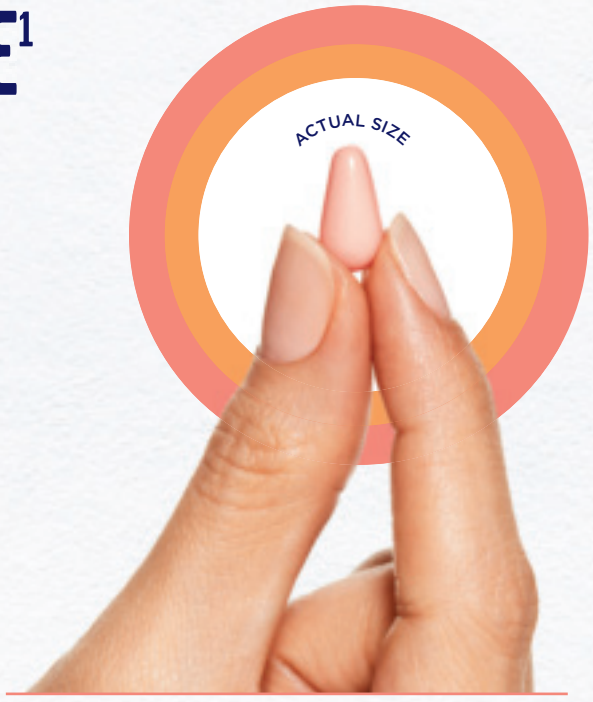
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

Imvexxy®
(estradiol vaginal inserts)
4 mcg • 10 mcg

DISCOVER A TREATMENT EXPERIENCE WITH

SIMPLICITY AT ITS CORE[1]

- THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES[1,2]
- PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)[1,3]
- MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED[1,3]



TO LEARN MORE AND REQUEST SAMPLES, VISIT IMVEXXYINFO.COM

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
- The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.
- Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS

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

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

References: 1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019. **2.** Data on file. Vaginal Estrogen PIs. **3.** Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause.* 2017;24(4):409-416.

TherapeuticsMD®
For Her. For Life.

IMVEXXY® (estradiol vaginal inserts)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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 (5.3) in full prescribing information].*

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].*

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].*

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].*

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg] relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].*

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

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2) 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.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15) in full prescribing information].*

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

CONTRAINDICATIONS

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 (e.g., stroke and myocardial infarction (MI)) or a history of these conditions; known anaphylactic reaction or angioedema with IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY (*Pharmacokinetics [12.3] in full prescribing information*). The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, estrogen with or without progestin 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.

Malignant Neoplasms

Endometrial Cancer

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 times 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 progestin 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 progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] *[see Clinical Studies (14.2) in full prescribing information].*

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. 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 use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

Ovarian Cancer

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.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

Other Warnings and Precautions include:

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Geriatric Use

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

Based on IVXY-LAB-20004.2
Revised: 04/2019

TherapeuticsMD®

IVXY-20054.3 09/2019

ON THE WEB
at mdedge.com/obgyn

WEB EXCLUSIVE

Confronting the epidemic of racism in ObGyn practice

PREETHA NANDI, MD, MPH;
VICTORIA WANG, MD;
ALEXIS GRIFFIN, MD;
AND MEGAN L. EVANS, MD, MPH

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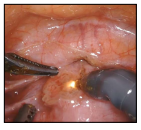
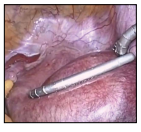


Isthmocele repair: Simultaneous hysteroscopy and robotic-assisted laparoscopy

SIERRA J. SEAMAN, MD;
CHETNA ARORA, MD;
AND ARNOLD P. ADVINCULA, MD



Laparoscopic transabdominal cerclage

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RENAE SHIBATA, MD;
OLIVIA MOSKOWITZ, MD;
GIANNI RODRIGUEZ-AYALA, MD;
AND MICHAEL L. NIMAROFF, MD

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EDITORIAL

New hormonal medical treatment is an important advance for AUB caused by uterine fibroids

Women with fibroids causing symptomatic abnormal uterine bleeding who choose to avoid a therapeutic procedure have a new hormonal treatment option

Robert L. Barbieri, MD
Editor in Chief, OBG Management
Chair, Obstetrics and Gynecology
Brigham and Women's Hospital
Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School

Uterine leiomyomata (fibroids) are the most common pelvic tumor diagnosed in women.[1] Women with symptomatic fibroids often report abnormal uterine bleeding (AUB) and pelvic cramping, fullness, or pain. Fibroids also may cause frequency of urination and contribute to fertility and pregnancy problems. Treatment options for the AUB caused by fibroids include, but are not limited to, hysterectomy, myomectomy, uterine artery embolization, endometrial ablation, insertion of a levonorgestrel intrauterine device, focused ultrasound surgery, radiofrequency ablation, leuprolide acetate, and elagolix plus low-dose hormone add-back (Oriahnn; AbbVie, North Chicago, Illinois).[1] Oriahnn is the most recent addition to our treatment armamentarium for fibroids and represents the first US Food and Drug Administration (FDA)-approved long-term hormonal option for AUB caused by fibroids.

Gene dysregulation contributes to fibroid development

Most uterine fibroids are clonal tumors, which develop following a somatic mutation in a precursor uterine myocyte. The somatic mutation causes gene dysregulation that stimulates cell growth resulting in a benign tumor mass. The majority of fibroids contain a mutation in one of the following 6 genes: *mediator complex subunit 12* (*MED12*), *high mobility group AT-hook* (*HMGA2* or *HMGA1*), *RAD51B*, *fumarate hydratase* (*FH*), *collagen type IV, alpha 5 chain* (*COL4A5*), or *collagen type IV alpha 6 chain* (*COL4A6*).[2]

Gene dysregulation in fibroids may arise following chromothripsis of the uterine myocyte genome

Chromothripsis is a catastrophic intracellular genetic event in which one or more chromosomes are broken and reassemble in a new nucleic acid sequence, producing a derivative chromosome that contains complex genetic rearrangements.[3] Chromothripsis is believed to occur frequently in uterine myocytes. It is unknown why uterine myocytes are susceptible to chromothripsis,[3] or why a catastrophic intracellular event such as chromothripsis results in preferential mutations in the 6 genes that are associated with myoma formation.

Estrogen and progesterone influence fibroid size and cell activity

Although uterine fibroids are clonal tumors containing broken genes, they are also exquisitely responsive to estradiol and progesterone. Estradiol and progesterone play an important role in regulating fibroid size and function.[4] Estrogen stimulates uterine fibroids to increase in size. In a hypoestrogenic state, uterine fibroids

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decrease in size. In addition, a hypoestrogenic state results in an atrophic endometrium and thereby reduces AUB. For women with uterine fibroids and AUB, a reversible hypoestrogenic state can be induced either with a parenteral GnRH-agonist analogue (leuprolide) or an oral GnRH-antagonist (elagolix). Both leuprolide and elagolix are approved for the treatment of uterine fibroids (see below).

Surprisingly, progesterone stimulates cell division in normal uterine myocytes and fibroid cells.[5] In the luteal phase of the menstrual cycle, uterine myocyte mitoses are more frequent than in the follicular phase. In addition, synthetic progestins appear to maintain fibroid size in a hypoestrogenic environment. In one randomized trial, women with uterine fibroids treated with leuprolide acetate plus a placebo pill for 24 weeks had a 51% reduction in uterine volume as measured by ultrasound.[6] Women with uterine fibroids treated with leuprolide acetate plus the synthetic progestin, oral medroxyprogesterone acetate 20 mg daily, had only a 15% reduction in uterine volume.[6] This finding suggests that synthetic progestins partially block the decrease in uterine volume that occurs in a hypoestrogenic state.

Further evidence that progesterone plays a role in fibroid biology is the observation that treatment of women with uterine fibroids with the antiprogestin ulipristal decreases fibroid size and reduces AUB.[7-9] Ulipristal was approved for the treatment of fibroids in many countries but not the United States. Reports of severe, life-threatening liver injury—some necessitating liver transplantation—among women using ulipristal prompted the European Medicines Agency (EMA) in 2020 to recommend that women **stop taking ulipristal.** In addition, the EMA recommended that **no woman should initiate ulipristal treatment at this time.**[10]

Leuprolide acetate

Leuprolide acetate is a peptide GnRH-agonist analogue. Initiation of leuprolide treatment stimulates gonadotropin release, but with chronic administration pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) decreases, resulting in reduced ovarian follicular activity, anovulation, and low serum concentration of estradiol and progesterone. Leuprolide treatment concomitant with iron therapy is approved by the FDA for improving red blood cell volume prior to surgery in women with fibroids, AUB, and anemia.[11] Among women with fibroids, AUB, and anemia, after 12 weeks of treatment, the hemoglobin concentration was ≥12 g/dL in 79% treated with leuprolide plus iron and 56% treated with iron alone.[11] The FDA recommends limiting preoperative leuprolide treatment to no more than 3 months. The approved leuprolide regimens are a maximum of 3 monthly injections of leuprolide 3.75 mg or a single injection of leuprolide 11.25 mg. Leuprolide treatment prior to hysterectomy surgery for uterine fibroids usually will result in a decrease in uterine size and may facilitate vaginal hysterectomy.

Elagolix plus estradiol plus norethindrone acetate (Oriahnn)

GnRH analogues cause a hypoestrogenic state resulting in adverse effects, including moderate to severe hot flashes and a reduction in bone mineral density. One approach to reducing the unwanted effects of hot flashes and decreased bone density is to combine a GnRH analogue with low-dose steroid hormone add-back therapy. Combining a GnRH analogue with low-dose steroid hormone add-back permits long-term treatment of AUB caused by fibroids, with few hot flashes and a minimal decrease in bone mineral density. The FDA recently has approved the combination of elagolix plus low-dose estradiol and norethindrone acetate (Oriahnn) for the long-term treatment of AUB caused by fibroids.

Elagolix is a nonpeptide oral GnRH antagonist that reduces pituitary secretion of LH and FSH, resulting in a decrease in ovarian follicular activity, anovulation, and low serum concentration of estradiol and progesterone. Unlike leuprolide, which causes an initial increase in LH and FSH secretion, the initiation of elagolix treatment causes an immediate and sustained reduction in LH and FSH secretion. Combining elagolix with a low dose of estradiol and norethindrone acetate reduces the side effects of hot flashes and decreased bone density. Clinical trials have reported that the combination of elagolix (300 mg) twice daily plus estradiol (1 mg) and norethindrone acetate (0.5 mg) once daily is an effective long-term treatment of AUB caused by uterine fibroids.

To study the efficacy of elagolix (alone or with estrogen-progestin add-back therapy) for the treatment of AUB caused by uterine fibroids, two identical trials were performed,[12] in which 790 women participated. The participants had a mean age of 42 years and were documented to have heavy menstrual bleeding (>80 mL blood loss per cycle) and ultrasound-diagnosed uterine fibroids. The participants were randomized to one of 3 groups:

- elagolix (300 mg twice daily) plus low-dose steroid add-back

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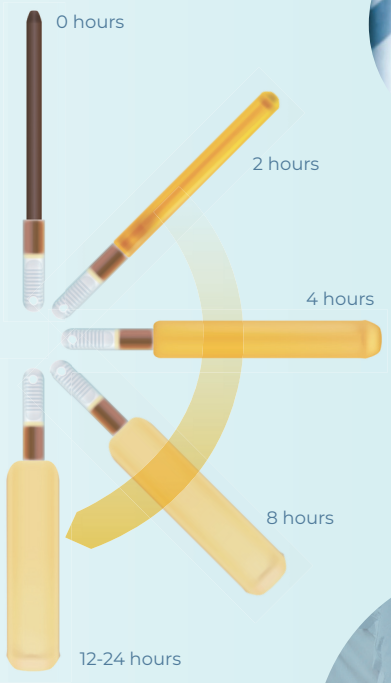

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Fibroids: Impact of age and race

Black women are more likely to develop fibroids and experience more severe fibroid symptoms. Obstetrician-gynecologists are experts in the diagnosis and treatment of fibroids. We play a key role in partnering with Black women to reduce fibroid disease burden.

Factors that increase the risk of developing fibroids include: increasing age, Black race, nulliparity, early menarche (<10 years of age), obesity, and consumption of red meat.[1] The Nurses Health Study II is the largest prospective study of the factors that influence fibroid development.[2] A total of 95,061 premenopausal nurses aged 25 to 44 years were followed from September 1989 through May 1993. Review of a sample of medical records demonstrated that the nurses participating in the study were reliable reporters of whether or not they had been diagnosed with fibroids. Based on a report of an ultrasound or hysterectomy diagnosis, the incidence rate for fibroids increased with age. Incidence rate per 1,000 women-years was 4.3 (age 25 to 29 years), 9.0 (30 to 34 years), 14.7 (age 35 to 39 years), and 22.5 (40 to 44 years). Compared with White race, Black race (but not Hispanic ethnicity or Asian race) was associated with an increased incidence of fibroids. Incidence rate per 1,000 women-years was 12.5 (White race), 37.9 (Black race), 14.5 (Hispanic ethnicity), and 10.4 (Asian race). The risk of developing fibroids was 3.25 times (95% CI, 2.71 to 3.88) greater among Black compared with White women after controlling for body mass index, age at first birth, years since last birth, history of infertility, age at first oral contraceptive use, marital status, and current alcohol use.[2]

Other epidemiology studies also report an increased incidence of fibroids among Black women.[3,4] The size of the uterus, the size and number of fibroids, and the severity of fibroid symptoms are greater among Black versus White women.[5,6] The molecular factors that increase fibroid incidence among Black women are unknown. Given the burden of fibroid disease among Black women, obstetrician-gynecologists are best positioned to ensure early diagnosis and to develop an effective follow-up and treatment plan for affected women.

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(1 mg estradiol and 0.5 mg norethindrone acetate once daily),

- elagolix 300 mg twice daily with no steroid add-back (elagolix alone), or
- placebo for 6 months.[12]

Menstrual blood loss was quantified using the alkaline hematin method on collected sanitary products. The primary endpoint was menstrual blood loss <80 mL per cycle as well as a ≥50% reduction in quantified blood loss from baseline during the final month of treatment. At 6 months, the percentage of women achieving the primary endpoint in the first trial was 84% (elagolix alone), 69% (elagolix plus add-back), and 9% (placebo). Mean changes from baseline in lumbar spine bone density were –2.95% (elagolix alone), –0.76% (elagolix plus add-back), and –0.21% (placebo). The percentage of women reporting hot flashes was 64% in the elagolix group, 20% in the elagolix plus low-dose steroid add-back group, and 9% in the placebo group. Results were similar in the second trial.[12]

The initial trials were extended to 12 months with two groups: elagolix 300 mg twice daily plus low-dose hormone add-back with 1 mg estradiol and 0.5 mg norethindrone acetate once daily (n = 218) or elagolix 300 mg twice daily (elagolix alone) (n = 98).[13] Following 12 months of treatment, heavy menstrual bleeding was controlled in 88% and 89% of women treated with elagolix plus add-back and elagolix alone, respectively. Amenorrhea was reported by 65% of the women in the elagolix plus add-back group. Compared with baseline bone density, at the end of 12 months of treatment, bone mineral density in the lumbar spine was reduced by -1.5% and -4.8% in the women treated with elagolix plus add-back and elagolix alone, respectively. Compared with baseline bone density, at 1 year following **completion** of treatment, bone mineral density in the lumbar spine was reduced

by -0.6% and -2.0% in the women treated with elagolix plus add-back and elagolix alone, respectively. Similar trends were observed in total hip and femoral neck bone density. During treatment with elagolix plus add-back, adverse effects were modest, including hot flushes (6%), night sweats (3.2%), headache (5.5%), and nausea (4.1%). Two women developed liver transaminase levels >3 times the upper limit of normal, resulting in one woman discontinuing treatment.[13]

Contraindications to Oriahnn include known allergies to the components of the medication (including the yellow dye tartrazine); high risk of arterial, venous thrombotic or thromboembolic disorders; pregnancy; known osteoporosis; current breast cancer or other hormonally-sensitive malignancies; known liver disease; and concurrent use of organic anion transporting polypeptide 1B1 inhibitors, which includes many HIV antiviral medications.[14] Undiagnosed AUB is a contraindication, and all women prescribed Oriahnn should have endometrial sampling before initiating treatment. Oriahnn should not be used for more than 24 months due to the risk of irreversible bone loss.[14] Systemic estrogen and progestin combinations, a component of Oriahnn, increases the risk for pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at increased risk for these events (such as women >35 years who smoke cigarettes and women with uncontrolled hypertension).[14] In two studies there was a higher incidence of depression, depressed mood, and/or tearfulness in women taking Oriahnn (3%) compared with those taking a placebo (1%).[14] The FDA recommends promptly evaluating women with depressive symptoms to determine the risks of initiating and continuing Oriahnn therapy. In two studies there was a higher risk of reported alopecia among women taking Oriahnn (3.5%) compared with placebo (1%).[14]

It should be noted that elagolix is approved for the treatment of pelvic pain caused by endometriosis at a dose of 150 mg daily for 24 months or 200 mg twice daily for 6 months. The elagolix dose for the treatment of AUB caused by fibroids is 300 mg twice daily for up to 24 months, necessitating the addition of low-dose estradiol-norethindrone add-back to reduce the frequency and severity of hot flashes and minimize the loss of bone density. Norethindrone acetate also protects the endometrium from the stimulatory effect of estradiol, reducing the risk of developing endometrial hyperplasia and cancer. Oriahnn is formulated as two different capsules. A yellow and white capsule contains elagolix 300 mg plus estradiol 1 mg and norethindrone acetate 0.5 mg to be taken in the morning, and a blue and white capsule contains elagolix 300 mg to be taken in the evening.

AUB caused by fibroids is a common problem in gyn practice

There are many procedural interventions that are effective in reducing AUB caused by fibroids. However, prior to the approval of Oriahnn there were no hormonal medications that were FDA approved for the long-term treatment of AUB caused by fibroids. Hence, Oriahnn represents an important advance in the hormonal treatment of AUB caused by fibroids and expands the treatment options available to our patients. ●

RBARBIERI@MDEDGE.COM

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

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HOW DO YOU FEEL ABOUT EXPECTANTLY MANAGING A WELL-DATED PREGNANCY PAST 41 WEEKS' GESTATION?
ROBERT L. BARBIERI, MD
(EDITORIAL; FEBRUARY 2019)

Is it reasonable to choose the age of 40 for proposing an anticipation of labor induction?

In physiologic ongoing pregnancies (whether they are spontaneous or autologous in vitro fertilization [IVF] or heterologous IVF), the evidence for anticipating labor induction based upon the only factor of age (after 40 years) is missing. Nonetheless, the number of women becoming pregnant at an older age is expected to increase, and from my perspective, to induce all physiologic pregnancies at term by 41 weeks and 5 days' gestation does not appear to be best practice. I favor the idea of all women aged 40 and older to start labor induction earlier (for instance, to offer labor induction, with proper informed consent, by 41+ 0 and not 41+ 5 through 42+ 0 weeks of pregnancy).

Luca Bernardini, MD
La Spezia, Italy

Dr. Barbieri responds

At Brigham and Women's Hospital in Boston, Massachusetts, our approach is to offer women ≥40 years of age induction of labor (IOL) at 39 weeks' gestation, unless there is an obstetric contraindication to IOL. We believe that IOL at 39 weeks' gestation is associated with a reduced risk of both cesarean delivery and a new diagnosis of hypertension.[1]

FEBRUARY 2019

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WHAT IS THE OPTIMAL HORMONAL TREATMENT FOR WOMEN WITH POLYCYSTIC OVARY SYNDROME?
ROBERT L. BARBIERI, MD
(EDITORIAL; JANUARY 2020)

OCs and spironolactone study

I often recommend oral contraceptives (OCs) containing drospirenone for patients with polycyctic ovary syndrome (PCOS)-associated mild acne and hirsutism—since OCs are already approved by the US Food and Drug Administration for acne, with similar effects as spironolactone. My patients seem to do well on an OC, and require only one medication. Of course, I would add spironolactone to the treatment regimen and switch OCs if she was not responding well.

Michael T. Cane, MD
Arlington, Texas

Dr. Barbieri responds

The Endocrine Society agrees with Dr. Cane's approach, recommending the initiation of monotherapy with an estrogen-progestin followed by the addition of spironolactone if 6 months of monotherapy produces insufficient improvement in dermatologic symptoms of PCOS, including hirsutism and acne. Most contraceptives contain 3 mg or 4 mg of drospirenone, which is thought to have antiandrogenic effects similar to spironolactone 25 mg. I believe that spironolactone 100 mg provides more complete and rapid resolution of the dermatologic symptoms caused by PCOS. Hence, I initiate both an estrogen-progestin contraceptive with spironolactone.

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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.

[†]In the pivotal study, screening colonoscopy was the reference method.[1]

[‡]Cologuard sensitivity, per stage of cancer: I: 90% (n=29); II: 100% (n=21); III: 90% (n=10); IV: 75% (n=4).[1]

[§]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.[1]

[‖]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.[1]

Reference: 1. 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.

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How effective is screening mammography for preventing breast cancer mortality?

An analysis of observational data from 76,630 women included in a breast cancer registry in Victoria, Australia, from 1982 to 2012 found that **mammography screening did not downstage breast cancer from advanced to early,** thus showing a lack of mortality benefit. All of the **decline in breast cancer mortality since 1994 was associated with adjuvant therapy uptake** with tamoxifen or chemotherapy.

Burton R, Stevenson C. Assessment of breast cancer mortality trends associated with mammographic screening and adjuvant therapy from 1986 to 2013 in the state of Victoria, Australia. JAMA Netw Open. 2020;3:e208249.

EXPERT COMMENTARY
Andrew M. Kaunitz, MD, is Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville; Medical Director and Director of Menopause and Gynecologic Ultrasound Services, UF Women's Health Specialists at Emerson, Jacksonville. He serves on the OBG MANAGEMENT Board of Editors.

Although recommending screening mammograms continues to represent the standard of care, studies from the United States and abroad have questioned their value.[1-3]

In the June issue of *JAMA Network Open*, Australian investigators assessed the relative impacts of mammography screening and adjuvant therapy on breast cancer mortality, using data from population-based studies from 1982 through 2013.[4] In recent decades, screening has increased substantially among Australian women.

Details of the study

Burton and Stevenson identified 76,630 women included in the Victorian Cancer Registry with invasive breast cancer in the state of Victoria, where women aged 50 to 69 are offered biennial screening.[4] During the study's time period, the use of adjuvant tamoxifen and chemotherapy increased substantially.

In the 31-year period assessed in this study, breast cancer mortality declined considerably. During the same period, however, the incidence of advanced breast cancer doubled.

These findings from Australia parallel those from the United States, Holland, and Norway, where the incidence of advanced breast cancer was stable or increased after screening mammography was introduced.[1-3]

According to Burton and Stevenson, the increased incidence of advanced cancer clarifies that screening mammography

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FAST TRACK

Studies from the United States and abroad have questioned the value of continuing to recommend screening mammograms

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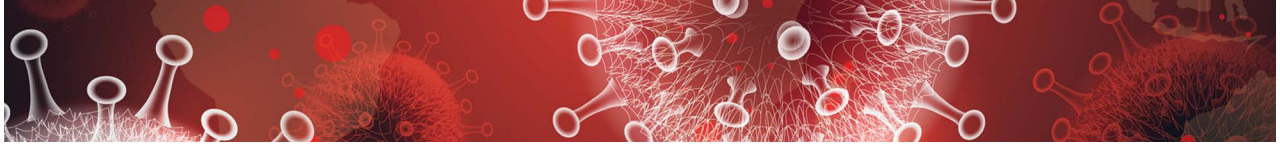

ROUNDTABLE

Restructuring health care delivery for the future: What we need to do post–COVID-19

Based on knowledge that has emerged from the COVID-19 pandemic, how would you change health care delivery if you could? Five experts share their thinking.

Expert panel featuring Barbara Levy, MD (Moderator); Scott D. Hayworth, MD; Janice Huckaby, MD; Errol R. Norwitz, MD, PhD, MBA; and Cynthia A. Pearson

Recently, OBG MANAGEMENT convened an expert panel of clinicians and thought leaders to discuss the changes needed in health care delivery—and in health care policy—that have risen to the forefront of consciousness as a result of the global COVID-19 pandemic. Here is that stimulating exchange moderated by Editorial Board member Dr. Barbara Levy.

Barbara Levy, MD: The disruption of the COVID-19 pandemic has given us an opportunity to consider how we would recraft the delivery of health care for women if we could. My goal for this discussion is to talk about that and see if we can incentivize people to make changes.

Cindy, what are women looking for in health care that they are not getting now?

What women want in health care

Cynthia A. Pearson: Women, like men, want a sense of assurance that health care can be provided in a safe way, and that can't be given completely right now.

Aside from that, women want a personal connection, ideally with the same provider. Many women are embracing telehealth, which came about because of this disruptive time, and that has potential that we can possibly mobilize around. One thing women don't always find is consistency and contact, and they would like that.

Scott D. Hayworth, MD: Women want to be listened to, and they want their doctors to take a holistic and individualized approach to their care. In-person visits are the ideal setting for this, but during the pandemic we have had to adapt to new modalities for delivering care: government regulations restricting services, and the necessity to limit the flow of patients into offices, has meant that we have had to rely on remote visits. CareMount Medical has been in the forefront of telehealth with our "Virtual Visit" technology, so we were well prepared, and our patients have embraced this truly vital option. We've ramped up capabilities significantly to deal with the surge in volume.

While our practice has been able to provide consistent and convenient access to care, this isn't the case in all areas of the country. Even before the pandemic, the cost of malpractice insurance has led to shortages of ObGyns; this deficit has been compounded by the closing of hospitals due to restrictions on services imposed to try to stem the spread of COVID-19. The affordability of care

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OBG Management Expert Panel

Barbara Levy, MD
Clinical Professor, Obstetrics and Gynecology
The George Washington University School of Medicine and Health Sciences
Washington, DC
Member, OBG Management Board of Editors

Scott D. Hayworth, MD
President and Chief Executive Officer
CareMount Medical, PC
Chappaqua, New York
Clinical Assistant Professor
Department of Obstetrics and Gynecology
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hofstra University
Hempstead, New York

Janice Huckaby, MD
Chief Medical Officer for Maternal-Child Health
Optum/UnitedHealth Group
Eden Prairie, Minnesota

Errol R. Norwitz, MD, PhD, MBA
President and Chief Executive Officer
Newton-Wellesley Hospital
Newton, Massachusetts
Professor, Obstetrics and Gynecology
Tufts University School of Medicine
Boston, Massachusetts

Cynthia A. Pearson
Executive Director
National Women's Health Network
Washington, DC

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has also been jeopardized by job losses and therefore of employer-provided insurance, following months of lockdowns.

Dr. Levy: To balance that long-term relationship with access and cost, clearly we are not delivering what is needed. Janice, at UnitedHealth you have experimented with some products and some different ways of delivering care. What are beneficiaries looking for?

Janice Huckaby, MD: There is a real thirst for digital content—everybody consults with Dr. Google. They are looking for reliable sources of clinical content. Ideally, that comes from their physician, but people access it in other ways as well.

I agree that women desire a personalized relationship. That is why we are seeing more communities of women, such as virtual pregnancy support groups, that have cropped up in the age of COVID-19. Women are not content with the idea of "I'm going to see my doctor, get my tummy measured, listen to the heartbeat, and go home." That model is done. Patients will look for practices that are accessible at convenient times and that can give them the personalized experience to make them feel well cared for and that offer them a long-term relationship.

One concern is that as more obstetric groups use laborists to do their deliveries at the hospital, I wonder whether we do a good job of forming that relationship on the front end, and when it comes to the delivery, will we drop the ball? The jury is out, but it's worth watching.

Dr. Levy: How do we as obstetrician-gynecologists get patients to consider that we are providing reliable information? There is so much disinformation out there.

Errol R. Norwitz, MD, PhD, MBA: I echo the sentiments discussed and I'll add that many women want care that is convenient, close to home, coordinated, and integrated—not fragmented. They want their providers and their office to anticipate and know who they are even before they arrive, to be prepared for the visit. And it's not only care for them, but also care for their families. Women are the gatekeepers to the health care system. They want a health care system in place that will care not just for each member separately but also for the family as an integrated whole.

To answer your question, Barbara, we have all been overwhelmed with the amount of data coming at us, both providers and

patients. Teaching providers how to synthesize and integrate the data and then present it to patients is quite a challenge. We have to instill this skill in our trainees, teach them how to absorb and present the data.

Consensus bodies can help in this regard, and ACOG (American College of Obstetricians and Gynecologists) has led the way in providing guidance around the management of pregnancy in the setting of COVID-19. Another reliable site for my trainees is UpToDate, which is easy to access. If a scientific paper comes out today, it will be covered in UpToDate tomorrow. Patients need someone who can synthesize the data and give it to them in little pieces, and keep it current.

Dr. Levy: We need to be a reliable source not only for medical information but also for referral to resources in the community for families and for women.

ObGyn services: Primary care or specialty?

Dr. Norwitz: That begs the question, who are we? Are we primary care providers or are we a subspecialty, or are we both?

Ms. Pearson: Women, particularly in their younger, middle reproductive years, see their ObGyn as a primary care provider. The way forward for the profession is to embrace the call that Barbara articulated, to know what other referral sources are available beyond other clinicians. We need to be aware of the social determinants of health—that there are times when the primary care provider needs to know the community well enough to know what is available that would make a difference for that person and her family.

Dr. Levy: Scott, how do you manage that?

Dr. Hayworth: As reimbursement models move rapidly toward value, practices that can undertake risk are in the best position to thrive; specialty providers relying solely on fee-for-service may well be unable to survive. The key for any ObGyn practice is to be of sufficient size and scope that it can manage the primary care for a panel of patients, the more numerous the better; being in charge of those dollars allows maximum control. ObGyns who subspecialize should seek to become members of larger groups, whether comprehensive women's health practices or multispecialty groups like ours at CareMount Medical, that manage the spectrum of care for their patients.

Dr. Levy: Janice, fill us in on some of the structures that exist now for ObGyns that they may be able to participate in—payment structures like the Women's Medical Home. Does UnitedHealth have anything like that?

Dr. Huckaby: Probably 3 or 4 exist now, but I agree that risk arrangements are perhaps a wave of the future. Right now, UnitedHealth has accountable care organizations (ACOs) that include ObGyns, a number of them in the Northeast. We also rolled out bundled payment programs.

Our hospital contracts have always had metrics around infection rates and elective deliveries before 39 weeks, and we will probably start seeing some of that put into the provider contracts as well.

There is a desire to move people into a risk-sharing model for payment, but part of the concern there is the infrastructure, because if you are going to manage risk, you need to have staff that can do care coordination. Care coordinators can ensure, for example, that people have transportation to their appointments, and thus address some of the social determinants in ways that historically have not been done in obstetrics.

The ACOs sometimes have given seed money for practices to hire additional staff to do those kinds of things, and that can help get practices started. Probably the people best positioned are in large multispecialty groups that can leverage case management and maybe support other specialties.

I do think we are going to see a move to risk in the future. Obstetrics has moved at a slower pace than we have seen in internal medicine and some other specialties.

Dr. Hayworth: The value model for reimbursement can only be managed via care coordination, maximizing efficacy and efficiency at every level for every patient. Fortunately for ObGyns, we are familiar with the value concept via bundling for obstetrical

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>
> —*Cynthia A. Pearson*

services covering prenatal to postpartum, including delivery. ObGyn practices need to prepare for a future in which insurers will pay for patient panels in which providers take on the risk for the entirety of care.

At CareMount Medical, we have embraced the value model as one of 40 Next Generation Medicare Accountable Care Organizations across the country. We've put in place the infrastructure, from front desk through back office, to optimize resource utilization. Our team approach includes both patient advocates and care coordinators who extend the capabilities of our physicians and ensure that our patients' needs, including well care, are met comprehensively.

Dr. Huckaby: One area that we sometimes leave out, whether we are talking about payment or a patient-centered medical home, is integration with behavioral health. Anxiety and depression are fairly rampant, fairly underdiagnosed, and woefully undertreated. I hope that our ObGyn practices of the future—and maybe this is the broadening into primary care—will engage and take the lead in addressing some of those issues, because women suffer. We need to embrace the behavioral aspect of care for the whole person more than we have.

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Physician training issues

Dr. Levy: I could not agree more. We have trained physicians to do illness care, not wellness care, and to be physician and practice centered, not patient centered. While we train medical students in hospital settings and in acute care, there's not much training in how to manage people or in the factors that determine whether someone is truly well, such as housing security and food security. We are not training physicians in nutrition or in mental health.

Errol, how do we help an ObGyn or women's health trainee to prepare for the ideal world we are trying to create?

Dr. Norwitz: It's a challenging question. I like to reference a remarkable piece by Atul Gawande in *The New Yorker*, in which he interviewed the CEO of the Cheesecake Factory restaurant chain, who in effect said that we've got it all wrong; there's no health in health care.[1] We don't manage health; we wait until people get sick and then we treat them. We have to put the health back into health care.

It has always been my passion to focus on preventative care. We need to reclaim our identity—I have never particularly liked the name "ObGyn," the term "women's health" may be more appropriate and help us focus on disease prevention—and we need to stand up for training programs that separate the O from the G.

Low-volume surgeons, who may do only 1 or 2 hysterectomies per year, can't maintain their proficiency, and many don't do enough cases to maintain their robotics privileges. I can foresee a time where labor and delivery units are like ICUs, where the people who work there do nothing but manage labor and perform deliveries using standardized bundles of practice. Such an approach will decrease variability in management and lead to improved outcomes.

We need to completely reframe how we train our pipeline providers to provide care in women's health. It would be difficult, take a lot of effort, and there would be pushback, I suspect, but that's where the field needs to go.

The ideal system redesign

Dr. Levy: Cindy, if you could start from scratch and design an ideal comprehensive system to better deliver care for women of all ages, what would that look like?

Ms. Pearson: I would design a system in which people at any life stage met with providers who were less trained in dealing with disease and more trained in the holistic approach to maintaining health. That might be a nurse practitioner or maybe a version of what Errol describes as a new way of training ObGyns. That's the initial interaction, and the person could be with someone for decades and deepen the relationship in that wonderful way. It would also have an avenue for the times when disease needed to be treated or when more specialized care would be

provided. And the financing would be worked out to support consistency.

Dr. Norwitz: We can learn from other countries. Singapore, with only 5.5 million people, has the best health care system in the world. They have a great model. Costa Rica and Cuba have completely redesigned their health care systems. You go through medical school in 2 or 3 years, and then you get embedded in the community. So you have doctors living in the community responsible for the health of their neighbors. They get to know people in the context in which they live and refer them on only when they need more than basic care. These countries have vastly superior outcome measures, and they spend less money on health care.

Dr. Levy: My dream, as we reinvent things, is that we could create a comprehensive Women's Medical Home where there's a hub and an opportunity to be centered on patients so they could reach us when needed.

Ideally we could create a structure with a central contact person—a nurse practitioner, a midwife, someone in family medicine or internal medicine—someone focused on women's health who has researched how inequities apply to women and women's health and the areas where research doesn't necessarily apply to women as just "smaller men." Then we would have the hub, and the spokes—those would be mental health care providers, surgeons, and people to provide additional services when needed.

The only way I can figure how to make that work from a payment perspective is with a prospective payment system, a per member, per month capitated payment structure. That way, ancillary and other services would be available, and overtesting and such would be disincentivized.

The question of payment

Dr. Hayworth: I agree. For every practice, the two key considerations in addressing the challenges of capitation are, first, that the team approach is essential, and, second, that providers appreciate that everything they do for their patients is reimbursed in a global payment.

At CareMount Medical, our team system embeds advanced practice professionals in our primary care and ObGyn offices. Everyone—physicians, midwives, nurse practitioners—practices at the top of their license. Our care coordinators ensure that our patients' health journeys are optimized from well care through specialized needs, engaging every member of the care team effectively.

To optimize our success in a risk model, we recognize that tasks and services that went without direct reimbursement in a fee-for-service arrangement are integral to producing the best outcomes for our patients. We examine everything we do from the perspective of how to provide the most advanced care in the most efficient manner. For example, we drive toward moving procedures from the hospital to the outpatient setting, and from the ambulatory surgical center to the office. This allows us maximal control of both quality and cost, with savings benefiting our group as well as the payers with whom we have contracts.

Dr. Norwitz: I have been fortunate to have trained and worked in 5 different countries on 3 continents. There's no question there are better health care systems out there. Some form of capitation is needed, whether it's value-based care or a risk-sharing arrangement. But how do you do it without a single payer? I don't think you can, but I'm ready to listen.

Dr. Hayworth: You can have capitation without a single payer; in fact, it's far better to have many payers compete to offer the greatest flexibility to both patients and providers. CareMount Medical has 650,000 patients who rely on us to provide their care with the utmost quality and affordability. In our Next Generation ACO, our Medicare patients have the benefit of care coordination in a team approach that saves our government money, and we are incentivized to do our best because some of those savings return to us.

The needs of Medicare patients, of course, are different from those in other age groups, and our contracts with other payers will reflect that distinction. There's no inherent reason why capitation has to equal "single payer." The benefits of the risk model are magnified by incentivizing all participants to provide maximum value.

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—Scott D. Hayworth, MD

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Ms. Pearson: I am going to comment on capitated care because I think educated consumers are well aware of the benefits of moving away from fee-for-service and bringing in some more sensible system. However, given the historical racial inequities and injustices, and lack of access and disparate treatment, capitation raises fear in the hearts of people whose communities have not gotten the care that they need.

The answer is not to avoid capitation, but to find a way for the profession to be seen more visibly as reflecting who they serve, and we know we can't change the profession's racial makeup overnight. That's a generation-long effort.

Dr. Levy: For capitation to work, there has to be value, you have to meet the quality metrics. Having served on the National Quality Forum on multiple different committees, I am convinced that we measure what is easy to measure, and we are not measuring what really matters to people. My thought is to embrace the communities that have been underserved to help us design the metrics for a capitated system that is meaningful to the people that we serve.

Ms. Pearson: On the West Coast, some people are leading efforts to create patient-centered metrics for respectful maternity care led by Black, indigenous, and people of color communities that are validated with solid research tools.

> "For capitation to work, there has to be value, you have to meet the quality metrics."
>
> —*Barbara Levy, MD*

Algorithms for care

Dr. Norwitz: Artificial intelligence (AI) may have a role to play. For example, I think we do a terrible job of caring for women in the postpartum period. We focus almost all of our care in the antepartum period and not postpartum. I am working with a group with a finance and banking background to try and risk-adjust patients in the antepartum, intrapartum, and postpartum period. We are developing algorithms using AI and deep learning technologies to risk-stratify patients and say, "This patient is low risk so can safely get obstetric care with a family medicine doctor or midwife. That patient requires consultation with a maternal-fetal medicine subspecialist or a general internist," and so on.

Ms. Pearson: As policy advocates, we are trying to get Medicaid postpartum coverage expanded to 12 months. Too many women fall into a coverage gap shortly after delivery; continued coverage would help improve postpartum outcomes. I am curious how an algorithm might help take better care of women postpartum.

Dr. Norwitz: Postpartum care is one of the greatest areas of need. I love the Dutch model. In the Netherlands, when a woman goes home after giving birth, a designated nurse comes home with her, teaches her how to breastfeed and how to bathe the baby, and assists with routine activities such as cooking and washing. And the nurse remains engaged for a prolonged period of time, paid for by the government. There are also other social welfare packages, such as a full 4-year or more maternity leave.

The solution is part political and part medical. We need to rethink our care model, and I don't think we provide enough postpartum care.

Dr. Hayworth: Errol made an excellent point about AI. There is a product that's being used in Europe and in some other parts of the world that can provide 85% of care through an algorithm without a patient even having to speak to a nurse or doctor. The company that offers the product claims a high level of patient satisfaction and a very low error rate.

We are a long way from the point at which—and I don't anticipate that we'll ever get there—AI fully replaces human providers, but there's enormous and growing potential for data aggregation and machine learning to enhance, exponentially, the capabilities and capacity of care teams.

The most immediate applications for AI in the United States are in diagnostics, pathology, and the mapping of protocols for patients with cancer who will benefit from access to investigational interventions and clinical trials. As we gain experience in those areas, acceptance and confidence will lead steadily to broader deployment of AI,

enhancing the quality of care and the efficiency of delivery and saving costs.

Dr. Norwitz: AI is a tool to assist providers. It is not going to replace us, which is the fear.

Ms. Pearson: From the consumer perspective, again, there is concern that if not enough data are available from Black, indigenous, and people of color, the levels won't start out in a good place. The criticism over mammography randomized controlled trials (RCTs) has existed for a long time. The big trials that got all the way out to mortality did not include enough women of color; and so women of color rightly say, "Why should we believe these guidelines developed on results of the RCTs?" My point is that because of historical inequity, logical solutions such as algorithms do not always work for communities that were previously excluded or mistreated.

Dr. Levy: Your point is incredibly well taken. That means that those of us researching and working with AI need to ensure that the data going in are representative, that we are not embedding implicit biases into the AI algorithms, which clearly has sometimes already happened. We have to be careful to embrace input from multiple sources that we have not thought of before.

As we look at an algorithm for managing a postpartum patient or a postoperative patient, have we thought about how she's managing her children at home after she goes home? What else is happening in her life? How can we impact her recovery in a positive way? We need to hear the voices of the people that we are trying to serve as we develop those algorithms.

Perspectives on future health care delivery

Dr. Levy: To summarize so far, we are thinking about a Woman's Medical Home, a capitated model of comprehensive care for women that includes mental health, social determinants, and home care. There are different models, but a payment structure where we would have the capital to invest in community services and in things that we think may make a difference.

Dr. Norwitz: I think the health care system of the future is not going to be based in large academic medical centers. It's going to be in community hospitals close to home. It's going to be in the home. And it will be provided by different types of practitioners, whose performances are tracked using more appropriate outcome metrics.

Dr. Levy: I also think we will have community health workers. While we haven't talked about rural health and access to care, there are some structural things we can do to reach rural communities with really excellent care, such as training community health workers and using telemedicine. It does require thinking through a different payment structure, though, because there really isn't money in the system to do that currently, at least to my knowledge.

Janice, do we have enough motivation to take care of women? Women are so underrepresented when we look at care models.

Dr. Huckaby: I do think there is hope, but it will truly take a village. While CMS (Centers for Medicare and Medicaid Services) has its innovation center in the Medicaid space, it's almost like we have to have the payers, the government, the specialty societies, and so on say that we need to do something better. I mention the government because it is not only a payer but also a regulator. They can help create some of these things.

There are opportunities with payers to say, "Let's move to this kind of model for that." But still, we are implementing change but on a fairly minor scale.

We could have the people who care about issues, help deliver the care, pay the bills, and so on say, "This is what we want to do," and then we could pilot them. It may be one type of pilot in a rural area and one type of pilot in an urban area, because they are going to differ, and do it that way and then scale it.

Telemedicine, or telehealth, is part of creating access. Even some nontraditional settings, such as retail store clinics, may work.

Dr. Levy: Cindy, is there any last thing you wanted to comment on?

Ms. Pearson: All the changes we have talked about require public policy change. Physicians become physicians to take care of people,

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>
> —*Errol R. Norwitz, MD, PhD, MBA*

not because they want to be policy wonks like us. We love policy because we see how it can benefit. To our readers I say be part of making this generational change in the profession and women's health care, get involved in policy, because these things can't happen without the policy changes.

Dr. Norwitz: That is so important. In most developed countries around the world, you get trained in medical school, the cost of training is subsidized, and in return you owe 2 years of service. In this country, if we subsidized the training of doctors and in return they owed us 2 years of primary care service based in the community or in an underserved area, they would get valuable clinical experience and wouldn't have so many loans to pay back. I think it is a policy that could work and could profoundly change the health care landscape in time.

Dr. Levy: And it would save a great deal of money. The reality is that if we subsidize medical education and in return required service in a national public health service, we would move providers out into rural areas. That would to some extent solve our rural problem. We would train people to think about diagnostic options when the resources are not unlimited, so that they will perhaps not order quite so many tests.

That policy change would foundationally allow for more minority students to become physicians and health care workers. If there were one thing we could do to begin to drive this change, that would be it.

Who would have thought a disruptive pandemic could affect the way people receive care, in bad and good ways? Some carriers, for example, are now paying for telehealth visits who previously did not.

Final thoughts

Dr. Hayworth: It's an exciting time to be in medicine and women's health: We are ushering in a new era in which we can fulfill the vision of comprehensive care, patient-focused and seamlessly delivered by teams whose capabilities are optimized by ever-improving technology. ObGyns, with our foundation in the continuum of care, have the experience and the sensibilities to adapt to the challenges of the value model, in which our success will depend on fully embracing our role as primary care providers.

Dr. Levy: Circling back to the beginning of our discussion, we talked about relationships, and developing deep relationships with patients is the internal reward and the piece that prevents us from burnout. It makes you feel good at the end of the day—or sometimes bad at the end of the day when something didn't go well. Restructuring the system in a way that gets us back to personalized relationship-centered care will benefit ObGyns and our patients.

I thank you all for participating in this thoughtful discussion. ●

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Candidiasis: The essentials of diagnosis and treatment

Vulvovaginal candidiasis is commonplace and may be caused by species other than *Candida albicans*. Serious complications may occur when infection occurs during pregnancy.

Kelly Kirkpatrick, BS, and Patrick Duff, MD

CASE Woman with vulvar itch and white vaginal discharge

A 26-year-old sexually active nulligravid woman requests evaluation for moderately intense "itching in the vagina and on the vulva." She uses combination oral contraceptives and has 2 current sexual partners. On physical examination, you note a thick, white, curd-like discharge that is adherent to the vaginal epithelium. The vulva is erythematous, and small "satellite lesions" are evident in the intertriginous folds.

- What is the most likely diagnosis?
- How should you treat this patient?

Approximately 75% of all women will have at least 1 episode of vulvovaginal candidiasis (VVC) in their lifetime.[1] *Candida albicans,* the most commonly identified organism in these infections, colonizes the vagina of many individuals commensally; higher rates of colonization occur in women with diabetes, obesity, recent use of broad-spectrum antibiotics, steroid use and immunosuppression, and in women who are pregnant. Of special interest, pregnant women have an increased risk of symptomatic infection, and they respond less favorably to conventional treatment regimens.[1]

Deconstructing *C albicans* and other species

Historically, in more than 90% of cases, *C albicans* is the principal cause of VVC. While it remains the most prevalent *Candida* species in the United States, over the last 15 years studies have demonstrated that in some countries, such as India and Nigeria, *C albicans* constitutes less than half of the cultured species in women with VVC. This observation may be due to the widespread availability and use of common antifungal medications, which leads to resistance and selection for resistant species.[1,2]

In asymptomatic women, vaginal colonies of *C albicans* grow in the yeast form. This condition is usually well tolerated by the host and does not cause a major immune response. In periods of stress for the host micro- and mycobiomes, however (dysbiosis, immune suppression, trauma), *C albicans* is induced into morphogenesis, proliferating and forming hyphae that are thought to activate the host immune response. The vaginal

Ms. Kirkpatrick is an MD/PhD student at the University of Florida College of Medicine, Gainesville.

Dr. Duff is Professor of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville.

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epithelium becomes sensitized to the presence of *C albicans* and recruits large numbers of neutrophils that, in turn, drive the pathophysiology of VVC.[3]

There is a theory that the separation of the urethra and anus by the vagina has exerted evolutionary pressure to maintain the presence of commensal *C albicans* yeast colonies in the vagina. *C albicans* exerts an antagonistic effect on many bacteria and, therefore, may act as a "microbiologic barrier" between the anus and the urethra to prevent urinary tract infections that, before the modern antibiotic era, may have caused serious morbidity and even mortality.[3]

Other organisms that cause VVC include *C glabrata, C parapsilosis,* and *C tropicalis*. Ex vivo experiments have shown that coinfection of *C albicans* with *C glabrata* enhances the ability of *C glabrata* to invade tissue.[2] *C glabrata* is more frequently resistant to commonly used antifungal compounds than *C albicans,*[2,4] which suggests that identifying the specific fungal pathogen is becoming increasingly important in planning targeted therapy.

FAST TRACK

Candida infection is characterized by acute vaginal and vulvar pruritus and thick, white, malodorous "cottage cheese" vaginal discharge

A common infection

While three-quarters of women will experience VVC at least once in their lifetime, between 40% and 45% will experience it more than once, and 5% to 8% will develop recurrent VVC. Among pregnant women, 15% will develop symptomatic VVC.[1,2] However, because VVC is not a reportable disease and antifungal medication is available over the counter without physician consultation, these numbers likely underestimate the true incidence of the infection.[4]

Complications in pregnancy

Vaginal infections, including VVC, bacterial vaginosis (BV), and trichomoniasis, may be associated with 40% of preterm deliveries.[5] The high concentrations of estrogen and progesterone during pregnancy create a uniquely glycogen-rich vaginal environment in which *Candida* species can flourish.[2,4] Even asymptomatic colonization of the vagina with *Candida* species has been associated with preterm labor, preterm birth, and low birth weight.[1,6] This association appears to have more severe consequences if VVC occurs in the second trimester compared with the first trimester.[6]

Additionally, congenital candidiasis of the newborn may result from intrauterine *Candida* infection or heavy maternal vaginal colonization at delivery, and the infection is evident within 24 hours of birth. It presents typically as oropharyngeal candidiasis (thrush) of the newborn.[1]

Clinical manifestations of infection

The classic manifestations of *Candida* infection are similar in both the pregnant and nonpregnant patient: acute vaginal and vulvar pruritus and thick, white, malodorous "cottage cheese" vaginal discharge.[1,4] Exercise caution, however, in treating presumptively based on these symptoms alone, especially in pregnancy, because they are not specific to candidiasis.[4] Vaginal discharge is not always present, and it may vary in appearance and odor. Pruritus is the most specific symptom of *Candida* infection, but studies show that it is an accurate predictor in only 38% of cases.[7]

Other common signs and symptoms include the sensation of burning, dysuria, dyspareunia, fissures, excoriations, and pruritus ani. Physical examination demonstrates erythema and swelling of labial, vulvar, and vaginal structures, with a normal cervix and an adherent white or off-white discharge. When the discharge is removed from the vaginal wall, small bleeding points may appear.[1,4]

Making the diagnosis

As mentioned, history alone is not sufficient to make a definitive diagnosis of candidiasis. The diagnosis should be made by examining vaginal secretions under a microscope or by culture.[4] A wet mount and KOH (potassium hydroxide) prep help differentiate VVC, BV, and trichomoniasis. Culture is particularly

TABLE Topical treatments for vulvovaginal candidiasis[8]

Drug	Dose	Duration
Clotrimazole	1% cream 5 g	Once daily, 7–14 days
Clotrimazole	2% cream 5 g	Once daily, 3 days
Miconazole	4% cream 5 g	Once daily, 3 days
Miconazole	200-mg vaginal suppository	Once a day for 3 days
Miconazole	1,200-mg vaginal suppository	Single administration
Tioconazole	6.5% ointment 5 g	Single application
Butoconazole	2% cream 5 g	Single application
Terconazole	0.8% cream 5 g	Once daily for 3 days
Terconazole	80-mg vaginal suppository	Once daily for 3 days

valuable in identifying less common fungal organisms, such as *C glabrata* and *C tropicalis*.

Vaginal pH testing is not conclusive for *Candida* because vaginal pH is normal in VVC. However, pH assessment can rule in other causative organisms if the value is abnormal (that is, elevated pH of 4.5 or greater with BV and trichomoniasis).[1]

Treatment options

Acute infection. A pregnant woman who tests positive for VVC may safely be treated in any trimester with a 7-day course of a topical azole.[8] If the patient prefers the convenience of oral therapy, after the first trimester, oral fluconazole, 150 mg on day 1 and day 3, may be used for treatment. Note that fluconazole has been associated with an increased risk of spontaneous abortion and cardiac septal defects when used in the first trimester.[1]

The Centers for Disease Control and Prevention recommends a number of topical treatments for VVC (**TABLE**).[8] Several of these drugs are available over the counter without a prescription. Topical azoles are more effective than nystatin in treating VVC, and posttreatment cultures are negative in up to 90% of treated patients.[8]

Recurrent infections. Recurrent VVC is defined as 4 or more episodes of symptomatic VVC within 12 months.[8] Typical first-line treatment of recurrent infections in nonpregnant patients is a 6-month course of fluconazole, 150 mg weekly.[9,10] As noted, however, fluconazole should not be used in the first trimester of pregnancy. It is acceptable therapy thereafter for patients who have troublesome recurrent or persistent infections.

Strategies for preventing recurrence

While it is logical to consider antimycotic prophylaxis in women with a history of recurring VVC and/or a significant number of known risk factors, data suggest that extended prophylaxis with an azole does not consistently achieve long-term elimination of vaginal *Candida* organisms after cessation of the azole.[9]

At-risk women should be counseled to make lifestyle adjustments, such as wearing breathable cotton clothing, particularly undergarments; promptly changing out of damp clothing; and forgoing the use of commercial intravaginal feminine hygiene products.

Recent research has shown that the use of *Saccharomyces cerevisiae*–based probiotics has promise for controlling the burden of *C albicans* in women receiving antifungal drugs for VVC and also for preventing recurrence; however, this approach has undergone limited testing in humans, and its efficacy and safety in pregnancy is unknown.[11] ●

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Fluconazole treatment, for acute or recurrent candidiasis, should not be used during the first trimester of pregnancy

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A pandemic playbook for residency programs in the COVID-19 era: Lessons learned from ObGyn programs at the epicenter

ObGyn education leaders from 5 academic medical centers within the epicenter of the COVID-19 pandemic summarize best practices based on their experience that can apply to many residency training programs

Julia Cron, MD; Katherine T. Chen, MD, MPH; Rini B. Ratan, MD; Abigail Ford Winkel, MD, MHPE; Karen Duncan, MD; and Erika Banks, MD

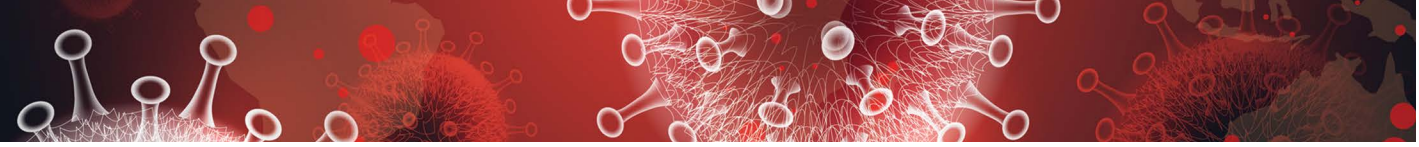
IN THIS ARTICLE

The 2020 pandemic of coronavirus disease 2019 (COVID-19) has presented significant challenges to the health care workforce.[1,2] As New York City and its environs became the epicenter of the pandemic in the United States, we continued to care for our patients while simultaneously maintaining the education and well-being of our residents.[3] Keeping this balance significantly strained resources and presented new challenges for education and service in residency education. What first emerged as an acute emergency has become a chronic disruption in the clinical learning environment. Programs are working to respond to the critical patient needs while ensuring continued progress toward training goals.

Since pregnancy is one condition for which healthy patients continued to require both outpatient visits and inpatient hospitalization, volume was not anticipated to be significantly decreased on our units. Thus, our ObGyn residency programs sought to expeditiously restructure our workforce and educational methods to address the demands of the pandemic. We were aided in our efforts by the Accreditation Council for Graduate Medical Education (ACGME) Extraordinary Circumstances policy. Our institutions were deemed to be functioning at Stage 3 Pandemic Emergency Status, a state in which "the increase in volume and/or severity of illness creates an extraordinary circumstance where routine care, education, and delivery must be reconfigured to focus only on patient care."[4]

As of May 18, 2020, 26% of residency and fellowship programs in the United States were under Stage 3 COVID-19 Pandemic Emergency Status.[5] Accordingly, our patient care delivery and educational processes were reconfigured within the context of Stage 3 Status, governed by the overriding principles of ensuring appropriate resources and training, adhering to work hour limits, providing adequate supervision, and credentialing fellows to function in our core specialty.

As ObGyn education leaders from 5 academic medical centers within the COVID-19 epicenter, we present a summary of best practices, based on our experiences, for each of the 4 categories of Stage 3 Status outlined by the ACGME. In an era of globalization, we must learn from pandemics, a call made after the Ebola outbreak in 2015.[6] We recognize that this type of disruption could



happen again with a possible second wave of COVID-19 or another emerging disease.[7] Thus, we emphasize "lessons learned" that are applicable to a wide range of residency training programs facing various clinical crises.

Ensuring adequate resources and training

Within the context of Stage 3 Status, residency programs have the flexibility to increase residents' availability in the clinical care setting. However, programs must ensure the safety of both patients and residents.

Measures to decrease risk of infection

One critical resource needed to protect patients and residents is personal protective equipment (PPE). Online instruction and in-person training were used to educate residents and staff on appropriate techniques for donning, doffing, and conserving PPE. Surgical teams were limited to 1 surgeon and 1 resident in each case. In an effort to limit direct contact with COVID-19 infected patients, the number of health care providers rounding on inpatients was restricted, and phone or video conversations were used for communication.

The workforce was modified to decrease exposure to infection and maintain a reserve of healthy residents who were working from home—anticipating that some residents would become ill and this reserve would be called for duty. Similar to other specialties, our programs organized the workforce by arranging residents into teams in which residents worked a number of shifts in a row.[8-12] Regular block schedules were disrupted and non-core rotations were deferred.

As surgeries were canceled and outpatient visits curtailed, many rotations required less resident coverage. Residents were reassigned from rotations where clinical work was suspended to accommodate increased staffing needs in other areas, while accounting for residents who were ill or on leave for postexposure quarantine. Typically, residents worked 12-hour shifts for 3 to 6 days followed by several days off or days working remotely. This team-based strategy decreased the number of residents exposed to COVID-19 at one time, provided time for recuperation, encouraged camaraderie, and enabled residents working remotely to coordinate care and participate in telehealth without direct patient contact.

Dr. Cron is Assistant Professor, Residency Program Director, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut.

Dr. Chen is Professor, Vice Chair of Education, Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York. She is an OBG MANAGEMENT Contributing Editor.

Dr. Ratan is Associate Professor, Residency Program Director, Vice Chair of Education, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York.

Dr. Ford Winkel is Associate Professor, Vice Chair for Education, Department of Obstetrics and Gynecology, New York University School of Medicine, New York, New York.

Dr. Duncan is Assistant Professor, Residency Program Director, Department of Obstetrics and Gynecology, New York University School of Medicine, New York, New York.

Dr. Banks is Professor, Vice Chair, Residency Program Director, Department of Obstetrics, Gynecology and Women's Health, Albert Einstein College of Medicine, New York, New York.

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The workforce was modified to decrease exposure to infection and maintain a reserve of healthy residents who were working from home—anticipating that some residents would become ill and this reserve would be called for duty

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To minimize high-risk exposure of pregnant residents or residents with underlying health conditions, these residents also worked remotely. Similar to other specialties, it was important to determine essential resident duties and enlist assistance from other clinicians, such as fellows, nurse practitioners, physician assistants, and midwives.

To protect residents and patients, maximizing testing of patients for COVID-19 was an important strategy. Based on early experience at 1 center with patients who were initially asymptomatic but later developed symptoms and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), universal testing was implemented and endorsed by the New York State COVID-19 Maternity Task Force.[13] Notably, 87.9% of patients who were positive for SARS-CoV-2 at the time of admission had no symptoms of COVID-19 at presentation. Because the asymptomatic carrier rate appears to be high in obstetric patients, testing of patients is paramount.[3,14] Finally, suspending visitation (except for 1 support person) also was instrumental in decreasing the risk of infection to residents.[13]

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This pandemic placed residency program directors in an unusual situation as frontline caregivers for their own residents

Resources for residents with COVID-19

This pandemic placed residency program directors in an unusual situation as frontline caregivers for their own residents. It was imperative to track residents with physical symptoms, conduct testing when possible, and follow the course of residents with confirmed or suspected COVID-19. As serious illness and death have been reported among otherwise healthy young people, we ensured that our homebound residents were frequently monitored.[15] At several of our centers, residents with COVID-19 from any program who chose to separate from their families were provided with alternative housing accommodations. In addition, some of our graduate medical education offices identified specific physicians to care for residents with COVID-19 who did not require hospitalization.

Deployment to other specialties

Several hospitals in the United States redeployed residents because of staffing shortages in high-impact settings.[12] It was important for ObGyns to emphasize that the labor and delivery unit functions as the emergency ward for pregnant women, and that ObGyn residents possess skills specific to the care of these patients.

For our departments, we highlighted that external redeployment could adversely affect our workforce restructuring and, ultimately, patient care. We focused efforts on internal deployment or reassignment as much as possible. Some faculty and fellows in nonobstetric subspecialty areas were redirected to provide care on our inpatient obstetric services.

Educating residents

To maintain educational efforts with social distancing, we used videoconferencing to preserve the protected didactic education time that existed for our residents before the pandemic. This regularly scheduled, nonclinical time also was utilized to instruct residents on the rapidly changing clinical guidelines and to disseminate information about new institutional policies and procedures, ensuring that residents were adequately prepared for their new clinical work.

Work hour requirements

The ACGME requires that work hour limitations remain unchanged during Stage 3 Pandemic Emergency Status. As the pandemic presented new challenges and stressors for residents inside and outside the workplace, ensuring adequate time off to rest and recover was critical for maintaining the resident workforce's health and wellness.

Thus, our workforce restructuring plans accounted for work hour limitations. As detailed above, the restructuring was accomplished by cohorting residents into small teams that remained unchanged for several weeks. Most shifts were limited to 12 hours, residents continued to be assigned at least 1day off each week, and daily schedules were structured to ensure at least 10 hours off

between shifts. Time spent working remotely was included in work hour calculations.

In addition, residents on "jeopardy" who were available for those who needed to be removed from direct patient care were given at least 1 day off per week in which they could not be pulled for clinical duty. Finally, prolonged inpatient assignments were limited; after these assignments, residents were given increased time for rest and recuperation.

Ensuring adequate supervision

The expectation during Stage 3 Pandemic Emergency Status is that residents, with adequate supervision, provide care that is appropriate for their level of training. To adequately and safely supervise residents, faculty needed training to remain well informed about the clinical care of COVID-19 patients. This was accomplished through frequent communication and consultation with colleagues in infectious disease, occupational health, and guidance from national organizations, such as the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention, and information from our state health departments.

Faculty members were trained in safe donning and doffing of PPE and infection control strategies to ensure they could safely oversee and train residents in these practices. Faculty schedules were significantly altered to ensure an adequate workforce and adequate resident supervision. Faculty efforts were focused on areas of critical need—in our case inpatient obstetrics—with a smaller workforce assigned to outpatient services and inpatient gynecology and gynecologic oncology. Many ObGyn subspecialist faculty were redeployed to general ObGyn inpatient units, thus permitting appropriate resident supervision at all times. In the outpatient setting, faculty adjusted to the changing demands and learned to conduct and supervise telehealth visits.

Finally, for those whose residents were deployed to other services (for example, internal medicine, emergency medicine, or critical care), supervision became paramount. We checked in with our deployed residents daily to be sure that their supervision on those services was adequate. Considering the extreme complexity, rapidly changing understanding of the disease, and often tragic patient outcomes, it was essential to ensure appropriate support and supervision on "off service" deployment.

Fellows functioning in core specialty

Anticipating the increased need for clinicians on the obstetric services, fellows in subspecialty areas were granted emergency privileges to act as attending faculty in the core specialty, supervising residents and providing patient care. On the other hand, some of those fellows, primarily in gynecologic oncology, were externally redeployed out of core specialty to internal medicine and critical care units. Careful consideration of the fellows' needs for supervision and support in these roles was essential, and similar support measures that were put in place for our residents were offered to fellows.

In conclusion

The COVID-19 pandemic has presented diverse and complex challenges to the entire health care workforce. Because this crisis is widespread and likely will be lengthy, a sustained and organized response is required.[16] We have highlighted unique challenges specific to residency programs and presented collective best practices from our experiences in ObGyn navigating these obstacles, which are applicable to many other programs.

The flexibility and relief afforded by the ACGME Stage 3 Pandemic Emergency Status designation allowed us to meet the needs of the surge of patients that required care while we maintained our educational framework and tenets of providing adequate resources and training, working within the confines of safe work hours, ensuring proper supervision, and granting attending privileges to fellows in their core specialty. ●

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Many ObGyn subspecialist faculty were redeployed to general ObGyn inpatient units, thus permitting appropriate resident supervision at all times

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Physician leadership: Racial disparities and racism. Where do we go from here?

Biftu Mengesha, MD, MAS; Kavita Shah Arora, MD, MBE, MS; and Barbara Levy, MD

Dr. Mengesha is Assistant Professor, University of California, San Francisco, and Medical Director, Inpatient Obstetrics at Zuckerberg San Francisco General, San Francisco, California.

Dr. Arora is Associate Professor, Department of Reproductive Biology, and Associate Professor, Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, Ohio.

Dr. Levy is Clinical Professor, Obstetrics and Gynecology, George Washington University School of Medicine and Health Sciences, and Principal, The Levy Group LLC, Washington DC. She serves on the OBG Management Board of Editors.

The destructive toll COVID-19 has caused worldwide is devastating. In the United States, the disproportionate deaths of Black, Indigenous, and Latinx people due to structural racism, amplified by economic adversity, is unacceptable. Meanwhile, the continued murder of Black people by those sworn to protect the public is abhorrent and can no longer be ignored. Black lives matter. These crises have rightly gripped our attention, and should galvanize physicians individually and collectively to use our privileged voices and relative power for justice. We must strive for engaged, passionate, and innovative leadership deliberately aimed toward antiracism and equity.

The COVID-19 pandemic has illuminated the vast inequities in our country. It has highlighted the continued poor outcomes our health and health care systems create for Black, Indigenous, and Latinx communities. It also has demonstrated clearly that we are all connected—one large community, interdependent yet rife with differential power, privilege, and oppression. We must address these racial disparities—not only in the name of justice and good health for all but also because it is a moral and ethical imperative for us as physicians—and SARS-CoV-2 clearly shows us that it is in the best interest of everyone to do so.

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First step: A deep dive look at systemic racism

What is first needed is an examination and acknowledgement by medicine and health care at large of the deeply entrenched roots of systemic and institutional racism in our profession and care systems, and their disproportionate and unjust impact on the health and livelihood of communities of color. The COVID-19 pandemic is only a recent example that highlights the perpetuation of a system that harms people of color. Racism, sexism, gender discrimination, economic and social injustice, religious persecution, and violence against women and children are age-old. We have yet to see health care institutions implement system-wide intersectional and antiracist practices to address them. Mandatory implicit bias training, policies for inclusion and diversity, and position statements are necessary first steps; however, they are not a panacea. They are insufficient to create the bold changes we need. The time for words has long passed. It is time to listen, to hear the cries of anguish and outrage, to examine our privileged position, to embrace change and discomfort, and most importantly to act, and to lead in dismantling the structures around us that perpetuate racial inequity.

How can we, as physicians and leaders, join in action and make an impact?

Dr. Camara Jones, past president of the American Public Health Association, describes 3 levels of racism:

- structural or systemic
- individual or personally mediated
- internalized.

Interventions at each level are important if we are to promote equity in health and health care. This framework can help us think about the following strategic initiatives.

1. Commit to becoming antiracist and engage in independent study. This is an important first step as it will form the foundations for interventions—one cannot facilitate

change without understanding the matter at hand. This step also may be the most personally challenging step forcing all of us to wrestle with discomfort, sadness, fear, guilt, and a host of other emotional responses. Remember that great change has never been born out of comfort, and the discomfort physicians may experience while unlearning racism and learning antiracism pales in comparison to what communities of color experience daily. We must actively work to unlearn the racist and anti-Black culture that is so deeply woven into every aspect of our existence.

Learn the history that was not given to us as kids in school. Read the brilliant literary works of Black, Indigenous, and Latinx artists and scholars on dismantling racism. Expand our vocabulary and knowledge of core concepts in racism, racial justice, and equity. Examine and reflect on our day-to-day practices. Be vocal in our commitment to antiracism—the time has passed for staying silent. If you are white, facilitate conversations about race with your white colleagues; the inherent power of racism relegates it to an issue that can never be on the table, but it is time to dismantle that power. Learn what acts of meaningful and intentional alliances are and when we need to give up power or privilege to a person of color. We also need to recognize that we as physicians, while leaders in many spaces, are not leaders in the powerful racial justice grassroots movements. We should learn from these movements, follow their lead, and use our privilege to uplift racial justice in our settings.

2. Embrace the current complexities with empathy and humility, finding ways to exercise our civic responsibility to the public with compassion. During the COVID-19 pandemic we have seen the devastation that social isolation, job loss, and illness can create. Suddenly those who could never have imagined themselves without food are waiting hours in their cars for food bank donations or are finding empty shelves in stores. Those who were not safe at home were suddenly imprisoned indefinitely in unsafe situations. Those who were comfortable, well-insured, and healthy are facing an invisible health threat, insecurity, fear, anxiety, and loss. Additionally, our civic institutions are failing. Those of us who always took our right to vote for granted are being forced to stand in hours'-long lines to exercise that right; while those who have been systematically disenfranchised are enduring even greater threats to their constitutional right to exercise their political power, disallowing them to speak for their families and communities and to vote for the justice they deserve. This may be an opportunity to stop blaming victims and recognize the toll that structural and systemic contributions to inequity have created over generations.

3. Meaningfully engage with and advocate for patients. In health and health care, we must begin to engage with the communities we serve and truly listen to their needs, desires, and barriers to care, and respond accordingly. Policies that try to address the social determinants of health without that engagement, and without the acknowledgement of the structural issues that cause them, however well-intentioned, are unlikely to accomplish their goals. We need to advocate as physicians and leaders in our settings for every policy, practice, and procedure to be scrutinized using an antiracist lens. To execute this, we need to:

- ask why clinic and hospital practices are built the way they are and how to make them more reflexive and responsive to individual patient's needs
- examine what the disproportionate impacts might be on different groups of patients from a systems-level
- be ready to dismantle and/or rebuild something that is exacerbating disparate outcomes and experiences
- advocate for change that is built upon the narratives of patients and their communities.

We should include patients in the creation of hospital policies and guidelines in order to shift power toward them and to be transparent about how the system operates in order to facilitate trust and collaboration that centers patients and communities in the systems created to serve them.

4. Intentionally repair and build trust. To create a safe environment, we must repair what we have broken and earn the trust of communities by uplifting their voices and redistributing our power to them in changing the systems and structures that have, for generations, kept Black, Indigenous, and Latinx people oppressed. Building trust requires first owning our histories of colonization, genocide, and slavery—now turned mass incarceration, debasement, and exploitation—that has existed for centuries. We as physicians need to do an honest examination of how we have eroded the trust of the very communities we care for since our profession's creation. We need to acknowledge, as a white-dominant profession, the medical experimentation on and exploitation of Black and Brown bodies, and how this formed the foundation for a very valid deep distrust and fear of the medical establishment. We need to recognize how our inherent

racial biases continue to feed this distrust, like when we don't treat patients' pain adequately or make them feel like we believe and listen to their needs and concerns. We must acknowledge our complicity in perpetuating the racial inequities in health, again highlighted by the COVID-19 pandemic.

5. Increase Black, Indigenous, and Latinx representation in physician and other health care professions' workforce. Racism impacts not only patients but also our colleagues of color. The lack of racial diversity is a symptom of racism and a representation of the continued exclusion and devaluing of physicians of color. We must recognize this legacy of exclusion and facilitate intentional recruitment, retention, inclusion, and belonging of people of color into our workforce. Tokenism, the act of symbolically including one or few people from underrepresented groups, has been a weapon used by our workforce against physicians of color, resulting in isolation, "othering," demoralization, and other deleterious impacts. We need to reverse this history and diversify our training programs and workforce to ensure justice in our own community.

6. Design multifaceted interventions. Multilevel problems require multilevel solutions. Interventions targeted solely at one level, while helpful, are unlikely to result in the larger scale changes our society needs to implement if we are to eradicate the impact of racism on health. We have long known that it is not just "preexisting conditions" or "poor" individual behaviors that lead to negative and disparate health outcomes—these are impacted by social and structural determinants much larger and more deleterious than that. It is critically important that we allocate and redistribute resources to create safe and affordable housing; childcare and preschool facilities; healthy, available, and affordable food; equitable and affordable educational opportunities; and a clean environment to support the health of all communities—not only those with the highest tax base. It is imperative that we strive to understand the lives of our fellow human beings who have been subjected to intergenerational social injustices and oppressions that have continued to place them at the margins of society. We need to center the lived experiences of communities of color in the design of multilevel interventions, especially Black and Indigenous communities. While we as physicians cannot individually impact education, economic, or food/environment systems, we can use our power to advocate for providing resources for the patients we care for and can create strategies within the health care system to address these needs in order to achieve optimal health. Robust and equitable social structures are the foundations for health, and ensuring equitable access to them is critical to reducing disparities.

Resources

- "So You Want to Talk about Race," Ijeoma Oluo
- "How to Be an Antiracist," Ibram X. Kendi
- "Between the World and Me," Ta-Nehisi Coates
- A conversation on race and privilege (Angela Davis and Jane Elliot) https://www.youtube.com/watch?reload=9&v=S0jf8D5WHoo
- Uncomfortable conversations with a Black man (Emmanuel Acho) https://www.youtube.com/watch?v=h8jUA7JBkF4

Commit to lead

We must commit to unlearning our internalized racism, rebuilding relationships with communities of color, and engaging in antiracist practices. As a profession dedicated to healing, we have an obligation to be leaders in advocating for these changes, and dismantling the inequitable structure of our health care system.

Our challenge now is to articulate solutions. While antiracism should be informed by the lived experiences of communities of color, the work of antiracism is not their responsibility. In fact, it is the responsibility of our white-dominated systems and institutions to change.

There are some solutions that are easier to enumerate because they have easily measurable outcomes or activities, such as:

- collecting data transparently
- identifying inequities in access, treatment, and care
- conducting rigorous root cause analysis of those barriers to care
- increasing diverse racial and gender representation on decision-making bodies, from board rooms to committees, from leadership teams to research participants
- redistribute power by paving the

Glossary of terms

Antiracism – defined as the work of actively opposing racism by advocating for changes in political, economic, and social life. Antiracism tends to be an individualized approach, and set up in opposition to individual racist behaviors and impacts.

Black Lives Matter – a political movement to address systemic and state violence against African Americans. Per the Black Lives Matter organizers: "In 2013, three radical Black organizers—Alicia Garza, Patrisse Cullors, and Opal Tometi—created a Black-centered political will and movement building project called "BlackLivesMatter. It was in response to the acquittal of Trayvon Martin's murderer, George Zimmerman. The project is now a member-led global network of more than 40 chapters. Members organize and build local power to intervene in violence inflicted on Black communities by the state and vigilantes. Black Lives Matter is an ideological and political intervention in a world where Black lives are systematically and intentionally targeted for demise. It is an affirmation of Black folks' humanity, our contributions to this society, and our resilience in the face of deadly oppression."

Implicit bias – also known as unconscious or hidden bias, implicit biases are negative associations that people unknowingly hold. They are expressed automatically, without conscious awareness. Many studies have indicated that implicit biases affect individuals' attitudes and actions, thus creating real-world implications, even though individuals may not even be aware that those biases exist within themselves. Notably, implicit biases have been shown to trump individuals stated commitments to equality and fairness, thereby producing behavior that diverges from the explicit attitudes that many people profess.

Othering – view or treat (a person or group of people) as intrinsically different from and alien to oneself. (From https://lexico.com.)

For a full glossary of terms, visit RacialEquityTools.org (https://www.racialequitytools.org/glossary#anti-black).

way for underrepresented colleagues to participate in clinical, administrative, educational, executive, and health policy spaces
- mentoring new leaders who come from marginalized communities.

Every patient deserves our expertise and access to high-quality care. We should review our patient panels to ensure we are taking steps personally to be just and eliminate disparities, and we should monitor the results of those efforts.

Be open to solutions that may make us "uncomfortable"

There are other solutions, perhaps those that would be more effective on a larger scale, which may be harder to measure using our traditional ways of inquiry or measurement. Solutions that may create discomfort, anger, or fear for those who have held their power or positions for a long time. We need to begin to engage in developing, cultivating, and valuing innovative strategies that produce equally valid knowledge, evidence, and solutions without engaging in a randomized controlled trial. We need to reinvent the way inquiry, investigation, and implementation are done, and utilize novel, justice-informed strategies that include real-world evidence to produce results that are applicable to all (not just those willing to participate in sponsored trials). Only then will we be able to provide equitable health outcomes for all.

We also must accept responsibility for the past and humbly ask communities to work with us as we struggle to eliminate racism and dehumanization of Black lives by calling out our actions or inaction, recognizing the impact of our privileged status, and stepping down or stepping aside to allow others to lead. Sometimes it is as simple as turning off the Zoom camera so others can talk. By redistributing power and focusing this work upon the narratives of marginalized communities, we can improve our system for everyone. We must lead with action within our practices and systems; become advocates within our communities, institutions, and profession; strategize and organize interventions at both structural and individual levels to first recognize and

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  from Jose Carugno, MD,
  and Laura Florez, MD

CONTINUED FROM PAGE 38

name—then change—the systems; and unlearn behaviors that perpetuate racism.

Inaction is shirking our responsibility among the medical community

Benign inaction and unintentional acquiescence with "the way things are and have always been" abdicates our responsibility as physicians to improve the health of our patients and our communities. The modern Hippocratic Oath reminds us: "I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm." We have a professional and ethical responsibility to ensure health equity, and thus racial equity. As physicians, as healers, as leaders we must address racial inequities at all levels as we commit to improving the health of our nation. We can no longer stand silent in the face of the violence, brutality, and injustices our patients, friends, family, neighbors, communities, and society as a whole live through daily. It is unjust and inhumane to do so.

To be silent is to be complicit. As Gandhi said so long ago, we must "be the change we wish to see in the world." And as Ijeoma Olua teaches us, "Anti-racism is the commitment to fight racism wherever you find it, including in yourself. And it's the only way forward." ●

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Pregnancy of unknown location: Evidence-based evaluation and management

Identifying pregnancy of unknown location early with a combination of screening modalities guides management of intrauterine or ectopic pregnancy

Iris G. Insogna, MD, and Paula C. Brady, MD

IN THIS ARTICLE

CASE Woman with bleeding in early pregnancy

A 31-year-old woman (G1P0) presents to the local emergency department (ED) due to bleeding in pregnancy. She reports a prior open appendectomy for ruptured appendix; she denies a history of sexually transmitted infections, smoking, and contraception use. She reports having regular menstrual cycles and trying to conceive with her husband for 18 months without success until now.

The patient reports that the previous week she took a home pregnancy test that was positive; she endorses having dark brown spotting for the past 2 days but denies pain. Based on the date of her last menstrual period, gestational age is estimated to be 5 weeks and 1 day. Her human chorionic gonadotropin (hCG) level is 1,670 mIU/mL. Transvaginal ultrasonography demonstrates a normal uterus with an endometrial thickness of 10 mm, no evidence of an intrauterine pregnancy (IUP), normal adnexa bilaterally, and scant free fluid in the pelvis.

Dr. Insogna is Fellow, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts.

Dr. Brady is Assistant Professor, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, Columbia University Fertility Center, New York, New York.

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Identifying and evaluating pregnancy of unknown location

A pregnancy of unknown location (PUL) is defined by a positive serum hCG level in the absence of a visualized IUP or ectopic pregnancy (EP) by pelvic ultrasonography.

Because of variations in screening tools and clinical practices between institutions and care settings (for example, EDs versus specialized outpatient offices), the incidence of PUL is difficult to capture. In specialized early pregnancy clinics, the rate is 8% to 10%, whereas in the ED setting, the PUL rate has been reported to be as high as 42%.[1-6] While approximately 98% to 99% of all pregnancies are intrauterine, only 30% of PULs will continue to develop as viable ongoing intrauterine gestations.[7-9] The remainder are revealed

as failing IUPs or EPs. To counsel patients, set expectations, and triage to appropriate management, it is critical to diagnose pregnancy location as efficiently as possible.

Ectopic pregnancy

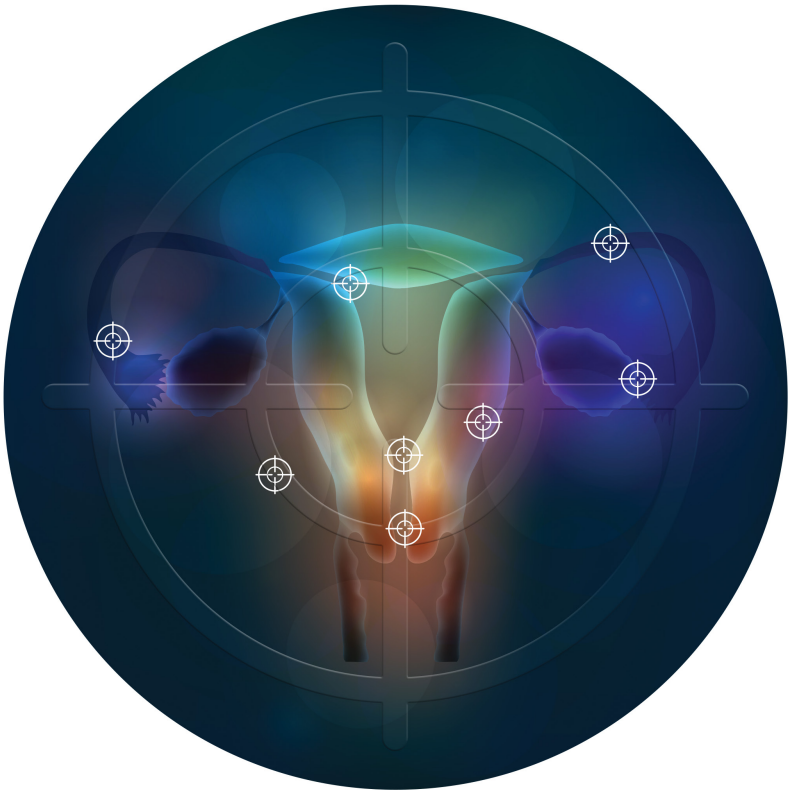
Ectopic pregnancies represent only 1% to 2% of conceptions (both spontaneous and through assisted reproduction) and occur most commonly in the fallopian tube, although EPs also can implant in the cornua of the uterus, the cervix, cesarean scar, and more rarely on the ovary or abdominal viscera.[10,11] Least common, heterotopic pregnancies—in which an IUP coexists with an EP—occur in 1 in 4,000 to 30,000 pregnancies, more commonly in women who used assisted reproduction.[11]

Major risk factors for EP include a history of tubal surgery, sexually transmitted infections (particularly *Chlamydia trachomatis*), pelvic inflammatory disease, conception with an intrauterine device in situ, and a history of prior EP or tubal surgery, particularly prior tubal ligation; minor risk factors include a history of infertility (excluding known tubal factor infertility) or smoking (in a dose-dependent manner).[11,12] The concern for an EP is heightened in patients with these risk factors.

Because of the possibility of rupture and life-threatening hemorrhage, EP carries a risk of significant morbidity and mortality.[13] Ruptured EPs account for approximately 2.7% of all maternal deaths each year.[14] When diagnosed sufficiently early in a stable patient, most EPs can be managed medically with methotrexate, a folic acid antagonist.[15] Ectopic pregnancies also may be managed surgically, and emergency surgery is indicated in women with evidence of EP rupture and intraperitoneal bleeding.

Intrauterine pregnancy

While excluding EP is critical, it is equally important to diagnose an IUP as expeditiously as possible to avoid inadvertent, destructive intervention. Diagnosis and management of a PUL can involve endometrial aspiration,



DIGITAL ILLUSTRATION BY JOHN J. DENAPOLI/TEFI/SHUTTERSTOCK

which would interrupt an IUP and should be avoided until the possibility of a viable IUP has been eliminated in desired pregnancies. The inadvertent administration of methotrexate, a known teratogen, to a patient with an undiagnosed viable IUP can result in miscarriage, elective termination, or a live-born infant with significant malformations, all of which expose the administering physician to malpractice litigation.[16,17]

In desired pregnancies, it is essential to differentiate between a viable IUP, a nonviable IUP, and an EP to guide appropriate management and ensure patient safety, whereas exclusion of EP is the priority in undesired pregnancies.

Tools for diagnosing pregnancy location

For diagnosing pregnancy location, serial hCG measurement, transvaginal pelvic ultrasonography, and outpatient endometrial

aspiration are all relevant clinical tools. Pregnancy location can be diagnosed with either direct visualization of an IUP or EP by ultrasonography or with confirmed pathology (chorionic villi or trophoblast cells) from endometrial aspiration (**FIGURE**). A decline in hCG to an undetectable level following endometrial aspiration also is considered sufficient to diagnose a failed IUP, even in the absence of a confirmatory ultrasonography.

Trending hCG values

In stable patients with PUL, serum hCG levels are commonly measured at 2-day intervals, ideally for a minimum of 3 values. Conventional wisdom dictates that in viable IUPs, the hCG level should roughly double every 2 days. However, more recent data suggest that the threshold for minimum expected hCG rise for an ongoing IUP should be far lower when the pregnancy is desired.[18] A less conservative cutoff can be considered when a pregnancy is not desired.

FAST TRACK

Recent data suggest that the threshold for minimum expected hCG rise for an ongoing IUP should be far lower when the pregnancy is desired

In a multisite cohort study of 1,005 women with PUL, a minimum hCG rise of 35% in 2 days captured the majority of IUPs, with a negative predictive value of 97.2% for IUP.[19] Of note, although the cutoff of 35% was selected to reduce the risk of misdiagnosing an IUP as an EP, 7.7% of IUPs (and 16.8% of EPs) were still misclassified, showing that hCG trends must be interpreted in the context of other clinical data, including ultrasonography findings and patient symptoms and history.

A follow-up study demonstrated that hCG rises are lower (but still within this normal range) when the initial hCG value is higher, particularly greater than 3,000 mIU/mL.[20]

Studies show that the rate of spontaneous hCG decline in failing IUPs ranges from 12% to 47% in 2 days, falling more rapidly from higher starting hCG values.[19,21] In a retrospective review of 443 women with spontaneously resolving PUL (presumed to be failing IUPs), the minimum 2-day decline in hCG was 35%.[22] Any spontaneous hCG decline less than 35% in 2 days in a PUL should raise physician concern for EP.

Conversely, EPs do not demonstrate predictable hCG trends and can mimic the hCG trends of viable or failing IUPs. Although typically half of EPs present with an increasing hCG value and half present with a decreasing hCG value, the majority (71%) demonstrate a slower rate of change than either a viable IUP or a miscarriage.[11] This slower change (plateau) should heighten the clinician's suspicion for an EP.

Progesterone levels

A progesterone level often is used to attempt to determine pregnancy viability in women who are not receiving progesterone supplementation, although it ultimately has limited utility. While far less sensitive than an hCG value trend, a serum progesterone level of less than 5 to 10 ng/mL is a rough marker of nonviable pregnancy.[23]

In a large meta-analysis of women with pain and bleeding, 96.8% of pregnancies with a single progesterone level of less than 10 ng/mL were nonviable.[23] When an inconclusive ultrasonography was documented in addition to symptoms of pain and bleeding, 99.2% of pregnancies with a progesterone level of less than 3.2 to 6 ng/mL were nonviable.

Progesterone's usefulness in assessing for a PUL is limited: While progesterone levels may indicate nonviability, they provide no indication of pregnancy location (intrauterine or ectopic).

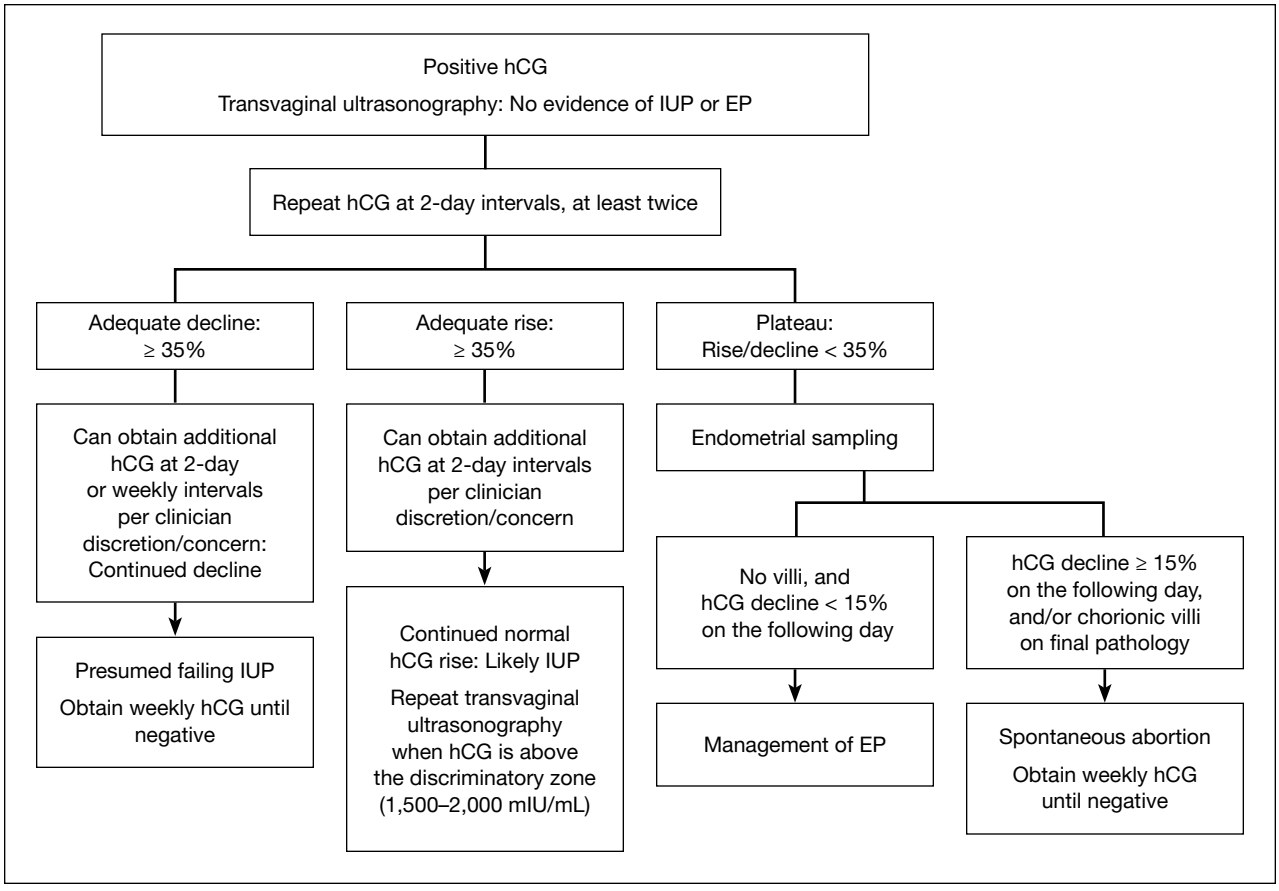
Alternative serologic markers

Various other reproductive and pregnancy-related hormones have been investigated for use in the diagnosis of pregnancy location in PULs, including activin A, inhibin A, pregnancy-associated plasma protein A (PAPP-A), placental-like growth factor, vascular endothelial growth factor, follistatin, and various microRNAs.[24,25] While research into these biomarkers is ongoing, none have been studied in prospective trials, and they are not for use in current clinical care.

Pelvic ultrasonography

Pelvic ultrasonography is a crucial part of PUL assessment. Transvaginal ultrasonography

FIGURE Steps in diagnosing pregnancy of unknown location



Abbreviations: EP, ectopic pregnancy; hCG, human chorionic gonadotropin; IUP, intrauterine pregnancy.

should be interpreted in the context of the estimated gestational age of the pregnancy and serial hCG values, if available; the patient's symptoms; and the sensitivity of the ultrasonography equipment, which also may be affected by variables that can reduce visualization, such as uterine fibroids and obesity.

The "discriminatory zone" refers to the hCG value above which an IUP should be visualized by ultrasonography. Generally, with an hCG value of 1,500 to 2,000 mIU/mL or greater, an IUP is expected to be seen with transvaginal sonography.[3,26] Many exceptions to the discriminatory zone have been reported, however, including multiple pregnancies, which will have a higher hCG value at an earlier gestational age. Even in singleton pregnancies, viable IUPs have been documented as developing from PULs with an elevated initial hCG value as high as 4,300 mIU/mL.[27] The discriminatory zone may vary among clinical hCG assays, and it also is affected by the quality and modernity of the ultrasonography equipment as well as by the ultrasonography operator's experience and skill.[28,29]

The estimated gestational age, based on either the last menstrual period or assisted reproduction procedure, provides a helpful data point to guide expectations for ultrasonography findings.[30] Using transvaginal ultrasonography in a normally progressing IUP, a gestational sac—typically measuring 2 to 3 mm—should be visualized at 5 weeks.[15,30] At approximately 5.5 weeks, a yolk sac measuring 3 to 5 mm should appear. At 6 weeks, an embryo with cardiac activity should be visualized.

In a pregnancy reliably dated beyond 5 weeks, the lack of an intrauterine gestational

sac is suspicious for, but not diagnostic of, an EP. Conversely, the visualization of a gestational sac alone (without a yolk sac) is insufficient to definitively exclude an EP, since a small fluid collection in the endometrium (a "pseudosac") can convincingly mimic the appearance of a gestational sac, and a follow-up ultrasonography should be performed in such cases.

Among patients without ultrasonographic evidence of an IUP, endometrial thickness has been posited as a way to differentiate between IUP and EP.[31,32] Evidence suggests that an endometrial stripe of at least 8 to 10 mm may be somewhat predictive of an IUP, while endometrial thickness below 8 mm is more concerning for EP. This clinical variable, however, has been shown repeatedly to lack sufficient sensitivity and specificity for IUP and should be considered only within the entire clinical context.

Endometrial aspiration

A persistently abnormal hCG trend and an ultrasonography without evidence of an IUP—particularly with an hCG value above the discriminatory zone and/or with reliable pregnancy dating beyond 5 to 6 weeks—is highly concerning for either a failing IUP or an EP. Once a viable desired IUP is excluded beyond reasonable doubt through these measures, endometrial aspiration to determine pregnancy location is a reasonable next step in PUL management.

Endometrial aspiration can identify a failing IUP by detection of trophoblasts or chorionic villi on pathology and/or by a decline of at least 15% in hCG, measured on the day of endometrial aspiration and again the following day. Endometrial aspiration is effective even in clinical care settings that do not have rapid pathologic analysis available, as hCG measurement before and within 24 hours after the procedure still can be performed.

Vacuum aspiration (electric or manual) in an operating room or office setting is an effective tool for diagnosing pregnancy location.[33,34] The use of an endometrial Pipelle for endometrial sampling (typically used for an office endometrial biopsy to diagnose hyperplasia or malignancy) is insufficient for determining pregnancy location.[35] For all patients managed with this protocol, the hCG value ideally should be followed until it is undetectable, regardless of whether an EP or failing IUP was diagnosed. In rare cases, an EP may be diagnosed by a late plateau in hCG values, following an initial decline consistent with a failing IUP.

Utility for diagnosis. Retrospective studies in patients with PUL following in vitro fertilization have established the utility of outpatient endometrial aspiration with a Karman cannula, followed by a repeat hCG measurement on the day after the procedure.[34,36] These data demonstrate that between 42% and 69% of women were ultimately diagnosed with a failed IUP following endometrial aspiration, thereby sparing them unnecessary exposure to methotrexate.

A decline in hCG levels of at least 15% within 24 hours after the procedure indicates that a failed IUP is the most likely diagnosis and further intervention is not indicated (although falling hCG values should be monitored for confirmation); confirmatory pathology with chorionic villi or trophoblasts was present in less than half of these women and is not necessary to diagnose a failed IUP.[36] Women diagnosed with a failed IUP after endometrial aspiration also benefitted from a shorter time to resolution of the nonviable pregnancy by approximately 2 weeks.[36]

Despite the efficacy of endometrial aspiration for the diagnosis of pregnancy location, recent data show that physicians have highly variable approaches to PUL with an hCG plateaued above the discriminatory zone: One-third would first perform endometrial aspiration, while one-third would give methotrexate without further diagnostics.[37] Academic physicians were 4 times more likely to recommend endometrial aspiration.[37]

Presumed EP. Following endometrial aspiration, if pathology does not confirm an intrauterine gestation and the hCG fails to decline by at least 15%, the diagnosis of a presumed EP is made.

For stable patients with neither evidence of intra-abdominal bleeding nor contraindications to methotrexate (such as blood

FAST TRACK

A decline in hCG levels of at least 15% within 24 hours of endometrial aspiration indicates that a failed IUP is the most likely diagnosis and further intervention is not indicated—although falling hCG values should be monitored for confirmation

dyscrasias, hepatic or renal insufficiency, active pulmonary or peptic ulcer disease, breastfeeding, or a known intolerance to the medication), methotrexate is recommended for medical management.[26] Following screening blood work that includes a complete blood count and liver function and renal function tests, the typical methotrexate dose is 50 mg/m^2 of body surface area. The single-dose regimen entails checking hCG on the day of methotrexate administration and again on days 4 and 7 thereafter. A minimum decline in hCG of 15% between days 4 and 7 indicates successful treatment; if the hCG decline is below 15%, the patient should receive an additional dose of methotrexate.

There are several published alternative regimens for methotrexate administration, including 2-dose and multidose regimens; the 2-dose protocol (2 doses within 7 days) may be more effective in women with higher hCG (> 3,000 mIU/mL) or known adnexal mass.[26,38]

Contraindications to methotrexate. In addition to strict medical contraindications to methotrexate, relative contraindications that indicate a higher risk of methotrexate failure include the presence of fetal cardiac activity, EP mass greater than 4 cm, and serum hCG above 5,000 mIU/mL.[26] Because of the potential risk of tubal rupture during medical management, relative contraindications also include patient inability to follow up as an outpatient and patient refusal of blood transfusion.[26] Patients with contraindications to methotrexate, hemodynamic instability, ultrasonographic or clinical evidence of EP rupture, or those electing for surgical management may be managed with laparoscopy.[11] Discussion of surgical management of EP is beyond the scope of this article.

Follow the hCG level. In patients with a failing IUP or an EP treated with methotrexate or salpingostomy, the hCG level should always be followed until it is negative, usually by weekly measurements once the diagnosis is made. In some cases, the hCG level may plateau after an initial decline, alerting the clinician to failed treatment for a known EP or the need for recategorization of a failed IUP as an EP.

CASE Concluded

The patient's second and third hCG measurements at 2-day intervals were 1,903 mIU/mL (14% rise) and 2,264 mIU/mL (16% rise). At that point, a repeat transvaginal ultrasonography showed no IUP, adnexal mass, or free fluid. The patient was counseled for outpatient endometrial aspiration, which was performed using manual vacuum aspiration. The serum hCG level on the morning of the procedure was 2,420 mIU/mL. On postprocedure day 1, the serum hCG level fell to 1,615 mIU/mL, a 33% decline. The patient was counseled that this decline in hCG indicated a failing IUP. The final pathologic analysis was returned 3 days later, showing no evidence of trophoblasts and chorionic villi. Regardless, the diagnosis of failing IUP remained given the rapid hCG decline; the tissue from the disrupted failing IUP was likely very scant or simply not drawn into the cannula. Serum hCG levels repeated at weekly intervals revealed ongoing decline, and after 4 weeks, the serum hCG was negative.

In summary

For women diagnosed with PUL, the primary goal is to distinguish an IUP from an EP to reduce the risk of EP rupture through expeditious diagnosis and treatment. In women for whom the pregnancy is desired, distinguishing a viable IUP from a nonviable IUP or an EP is the more specific goal to avoid intervention on a viable IUP (with methotrexate or endometrial aspiration). In women with abnormal hCG trends and indeterminate ultrasonography results (particularly with a serum hCG above the discriminatory zone), outpatient endometrial aspiration is a highly effective way to determine pregnancy location, which dictates further treatment. ●

FAST TRACK

The primary goal for women with PUL is to distinguish an IUP from an EP to reduce the risk of EP rupture through expeditious diagnosis and treatment

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is not responsible for declining breast cancer mortality, but all of the decline in mortality can be attributed to increased uptake of adjuvant therapy.

The authors concluded that since screening mammography does not reduce breast cancer mortality, state-sponsored screens should be discontinued.

Study strengths and limitations

Relevant data for this study were obtained from large population-based surveys for premenopausal and postmenopausal women with breast cancer.

The authors noted, however, that this analysis of observational data examining time trends across the study period can show only associations among breast cancer mortality, mammography screening participation, and adjuvant therapy uptake, and that causality can only be inferred.

The study in perspective

Although some will view the findings and recommendations of these Australian authors with skepticism or even hostility, I view their findings as good news—we have improved the treatment of breast cancer so dramatically that the benefits of finding early tumors with screening mammography have become attenuated.

Although it is challenging given the time constraints of office visits, I try to engage in shared decision making with my patients regarding when to start and how often to have screening mammography. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Given our evolving understanding regarding the value of screening mammograms, it is time to stop pressuring patients who are reluctant or unwilling to undergo screening. Likewise, insurance companies and government agencies should stop using screening mammography as a quality metric.

ANDREW M. KAUNITZ, MD

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INDEX OF ADVERTISERS

PRODUCT Update

NEW CERVICAL DILATOR

Hologic, Inc. announces the launch of the **Definity Cervical Dilator**, allowing tenaculum-free access to the uterine cavity, which lessens patient discomfort and reduces the risk of perforation during dilation, says **Hologic**. The dilator uses SureAccess—an expandable balloon technology designed to eliminate multiple passes and ensure safety during insertion, even for patients with complex or challenging cervical anatomy. **Definity Cervical Dilator** is not intended for use during induction of labor; some examples for its use include treatment of cervical stenosis, intrauterine device placement and removal, uterine tissue removal, diagnostic hysteroscopy, and operative hysteroscopy. Use of the system is contraindicated in patients with active genital tract infection, pelvic structure abnormality preventing device passage, or invasive cervical cancer. The **Definity Cervical Dilator** is now available across the United States in 5 mm, 7 mm, and 9 mm sizes.

FOR MORE INFORMATION, VISIT: https://www.hologic.com/

LIGHT DEVICE FOR HAIR REJUVENATION

Pattern hair loss (androgenetic alopecia) affects about 80 million men and women in the United States. In women, the hair loss typically occurs as thinning or widening of the midline. **Revian, Inc.** is focused on improving overall scalp health by stimulating the body's natural processes for hair and skin rejuvenation with light therapy. **REVIAN RED**, a dual-wavelength LED hair growth cap, has successfully demonstrated the ability to stop hair loss and subsequently grow new hair, says **Revian**. In a recent clinical trial, women who were at least 80% compliant with wearing **REVIAN RED** (versus a placebo cap with no light therapy) for 10 minutes per day had a mean improvement of 26.3 hairs/cm^2. Scalp irritations were assessed during the trial, with patient-reported itching and burning/stinging treated with at-home therapies.

The **REVIAN RED** wireless cap system is controlled by a mobile app and is US Food and Drug Administration (FDA) cleared as a hair loss treatment for men and women. The mechanism of action for improved scalp symptoms, says **Revian**, is the patented dual-wavelength light, which releases nitric oxide and is proposed to be anti-inflammatory.

The **REVIAN RED** system is indicated to treat androgenetic alopecia and to promote hair growth in men with Norwood-Hamilton classifications of IIa–V patterns of hair loss and to treat androgenetic alopecia and promote hair growth in women with Ludwig-Savin Scale I-1 to I-4, II-1, II-2 or frontal patterns of hair loss; both with Fitzpatrick Skin Types I–IV.

FOR MORE INFORMATION, VISIT: https://www.revian.com/

SUI TREATMENT

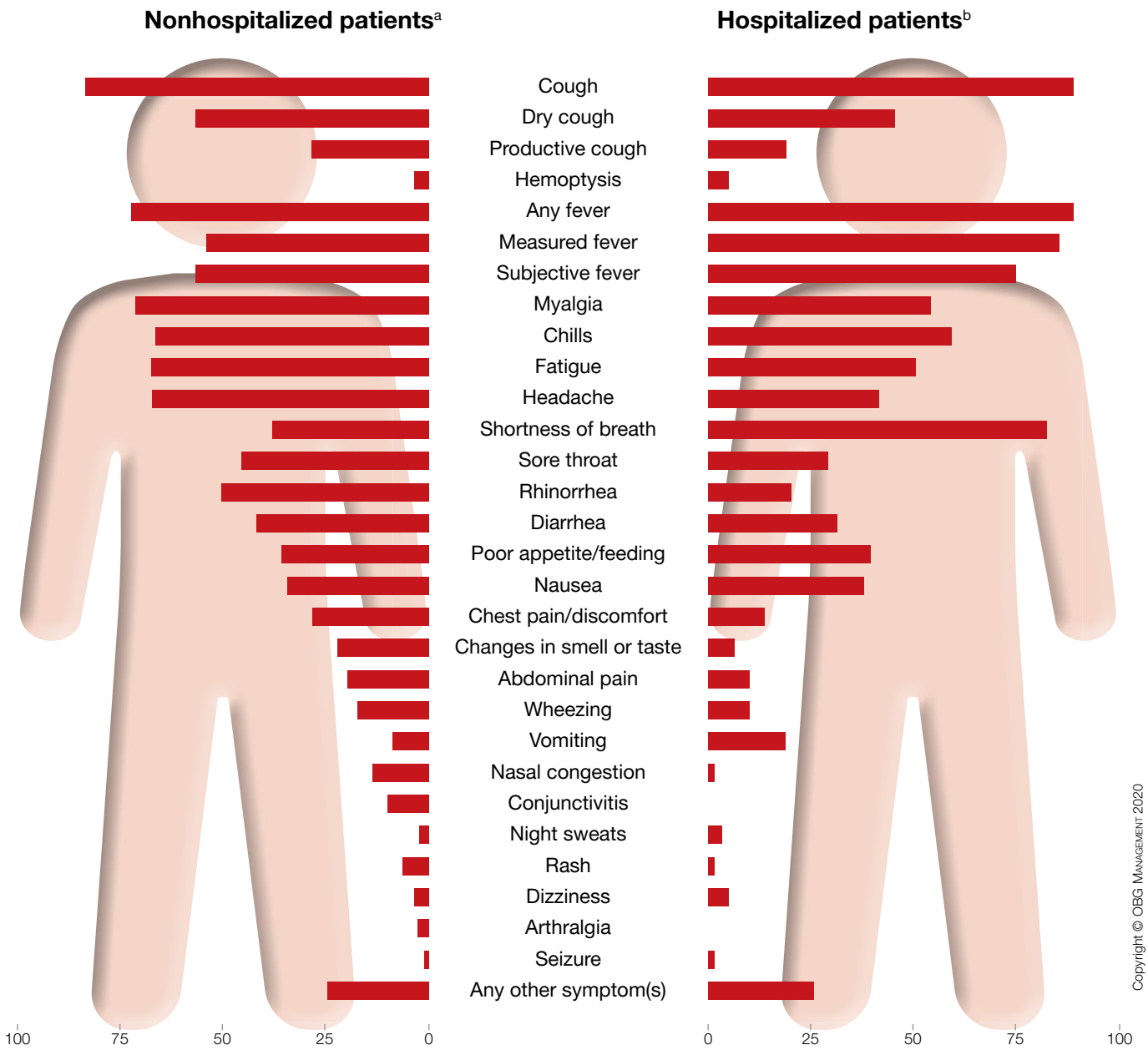
ELITONE from **Elidah** is the first transcutaneous pelvic floor muscle stimulation treatment for stress urinary incontinence (SUI). It is FDA cleared and works to train women to perform Kegel techniques by naturally contracting the correct pelvic floor muscles and surrounding tissues. The device is placed where a pad would go, according to **Elidah**, with conductive gel areas within the device delivering electrical muscle stimulation. Twenty-minute treatments 4 to 5 times per week are recommended, with improved SUI symptoms, depending on severity, for many women in 6 weeks. Three-quarters of women had significant reduction in daily leaks after 6 weeks of self-administered treatment with **ELITONE**, reports the manufacturer.

Elidah says that **ELITONE** is ideal for women with mild to moderate SUI symptoms who would benefit from pelvic floor muscle training, including those who are resistant to intravaginal treatments, need postpartum care, or have limited access to physical therapy. The device is contraindicated in women who have an implanted cardiac device, cancer, epilepsy, or recent pelvic floor surgery.

FOR OTHER CONTRAINDICATIONS AND MORE INFORMATION, VISIT: https:/elitone.com/

Reported COVID-19 symptoms by hospitalization status

What are the reported symptoms of nonhospitalized patients with laboratory-confirmed SARS-COV-2? Common symptoms reported between January and April 2020, among a convenience sample of 164 patients from across the United States, were fever, cough, and shortness of breath (96%). Other commonly reported symptoms included gastrointestinal symptoms, chills, myalgia, headache, and fatigue.



[a]Age ≥18; n = 81.
[b]Age ≥18; n = 57.

Source: Burke RM, Killerby ME, Newton S, et al. Symptom profiles of a convenience sample of patients with COVID-19—United States, January–April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:904-908.

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