MDEDGE.COM/OBGYN | VOL 32, NO 12 | DECEMBER 2020

# OBG MANAGEMENT

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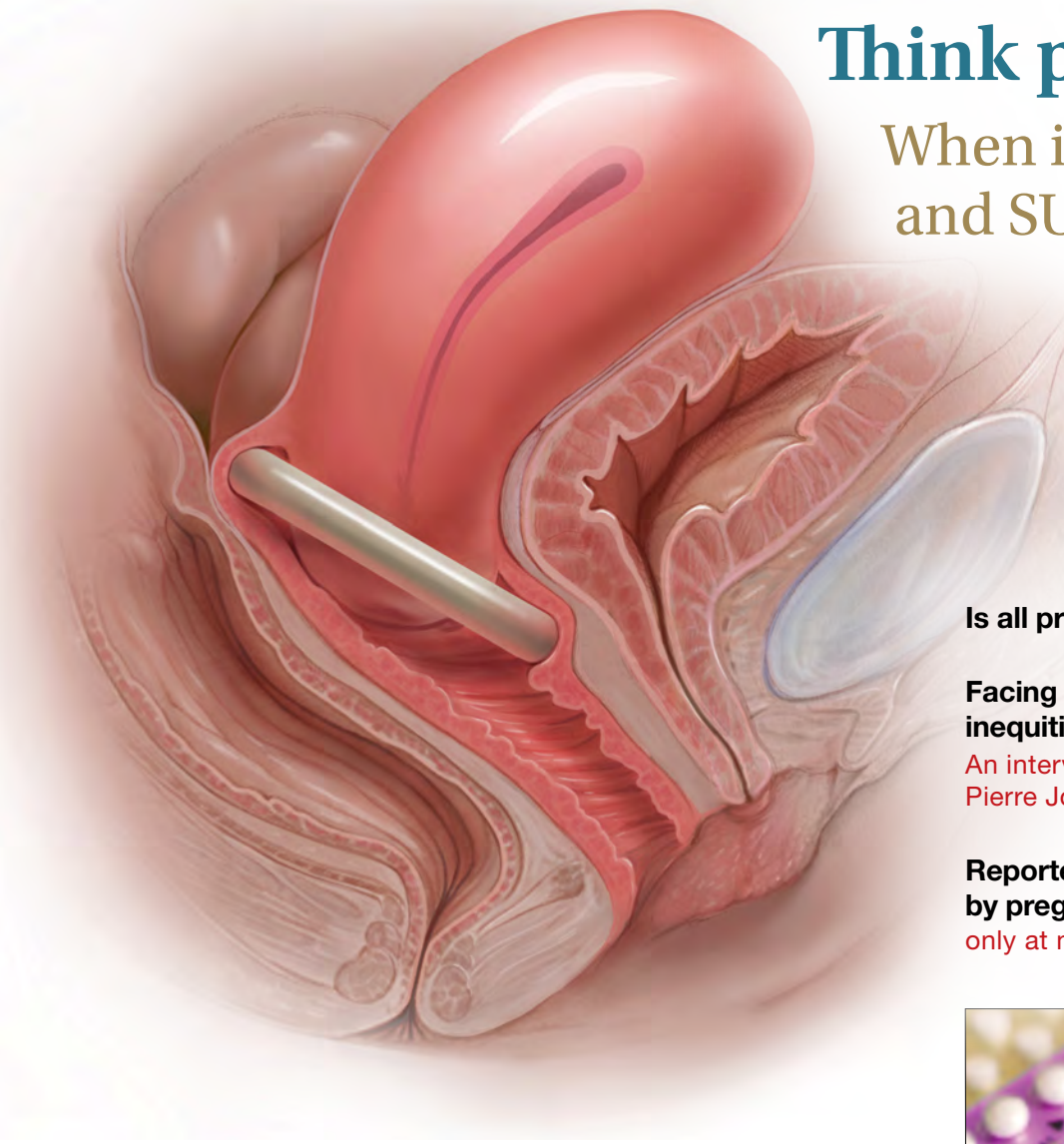
**Reducing endometrial cancer risk in obese postmenopausal women**
Robert L. Barbieri, MD

**Updates in bone health**

**Mifepristone restrictions lifted during pandemic**



## Think pessary first

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## IMPORTANT SAFETY INFORMATION

**WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**
***See full prescribing information for complete boxed warning.***

- **Females over 35 years old who smoke should not use ANNOVERA.**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use.**

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

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

- Other warnings include: gallbladder disease; depression; cervical cancer; increased serum concentrations of binding globulins; hereditary angioedema; chloasma (females who tend to develop chloasma should avoid exposure to the sun or UV radiation while using ANNOVERA); toxic shock syndrome (TSS) (if a patient exhibits symptoms of TSS, remove ANNOVERA, and initiate appropriate medical treatment); vaginal use (ANNOVERA may not be suitable for females with conditions that make the vagina more susceptible to vaginal irritation or ulceration).

## ADVERSE REACTIONS

The most common adverse reactions reported in at least 5% of women who received ANNOVERA were: headache/migraine, nausea/vomiting, vulvovaginal mycotic infection/candidiasis, lower/upper abdominal pain, dysmenorrhea, vaginal discharge, urinary tract infection, breast pain/tenderness/discomfort, bleeding irregularities including metrorrhagia, diarrhea, and genital pruritus.

## DRUG INTERACTIONS

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

## INDICATION

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

Limitations of Use: ANNOVERA has not been adequately studied in females with a body mass index >29 kg/m$^2$.

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

**References: 1.** Annovera® [Full Prescribing Information]. Boca Raton, FL: TherapeuticsMD, Inc; 2020. **2.** Merkatz RB, Plagianos M, Hoskin E, et al. Acceptability of the Nestorone®/ethinyl estradiol contraceptive vaginal ring: development of a model; implications for introduction. *Contraception*. 2014;90(5):514–521. doi:10.1016/j.contraception.2014.05.015. **3.** Kumar N, Koide SS, Tsong YY, Sundaram K. Nestorone®: a progestin with a unique pharmacological profile. *Steroids*. 2000;65:629–636.

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ANVA-20142.2 09/2020

**ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system)**

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

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

**WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**

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

## INDICATIONS AND USAGE

ANNOVERA is indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use: ANNOVERA has not been adequately studied in females with a BMI >29 kg/m$^2$.

## DOSAGE AND ADMINISTRATION

One ANNOVERA is inserted in the vagina. The vaginal system must remain in place continuously for 3 weeks (21 days) followed by a 1-week (7-day) vaginal system-free interval. One vaginal system provides contraception for thirteen 28-day cycles (1 year). Follow instructions for starting ANNOVERA, including switching from other contraceptive methods, and use after abortion, miscarriage, or childbirth *[see How to Start ANNOVERA (2.2) in PI]*.

Contraceptive efficacy of ANNOVERA may be reduced if a woman deviates from the recommended use. If ANNOVERA is out of the vagina for more than 2 continuous hours or more than 2 cumulative hours during the 21 days of continuous use, then back-up contraception, such as male condoms or spermicide, should be used until the vaginal system has been in the vagina for 7 consecutive days.

## CONTRAINDICATIONS

ANNOVERA is contraindicated in females who are known to have the following conditions: • A high risk of arterial or venous thrombotic diseases. Examples include females who are known to: smoke, if over age 35; have current or history of deep vein thrombosis or pulmonary embolism; have cerebrovascular disease; have coronary artery disease; have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation); have inherited or acquired hypercoagulopathies; have uncontrolled hypertension or hypertension with vascular disease; have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease, or other end-organ damage, or diabetes mellitus of >20 years duration; have headaches with focal neurological symptoms, migraine headaches with aura, or are over age 35 with any migraine headaches. • Current or history of breast cancer or other estrogen- or progestin-sensitive cancer. • Liver tumors, acute hepatitis, or severe (decompensated) cirrhosis. • Undiagnosed abnormal uterine bleeding. • Hypersensitivity to any of the components of ANNOVERA. Hypersensitivity reactions reported include: throat constriction, facial edema, urticaria, hives, and wheezing. • Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for alanine transaminase (ALT) elevations.

## WARNINGS AND PRECAUTIONS

**Thromboembolic Disorders and Other Vascular Conditions**

Females are at increased risk for a venous thrombotic event (VTE) when using ANNOVERA.

Stop ANNOVERA if a thrombotic or thromboembolic event occurs, or unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. Stop ANNOVERA at least 4 weeks before and through 2 weeks after major surgery. Start ANNOVERA no earlier than 4 weeks after delivery in females who are not breastfeeding. Before starting ANNOVERA, consider history and risk factors of thrombotic or thromboembolic disorders. ANNOVERA is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases.

Arterial Events

Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years. CHCs increase the risk of cardiovascular events and cerebrovascular events, such as stroke and myocardial infarction. The risk is greater among older females (>35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

Venous Events

The use of CHCs increases the risk of VTE, such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs. The rates of VTE are even greater during pregnancy, and especially during the postpartum period. The risk of VTE is highest during the first year of CHC use and when restarting hormonal contraception following a break of 4 weeks or longer. The risk of VTE due to CHCs gradually disappears after use is discontinued.

**Liver Disease**

Impaired Liver Function

ANNOVERA is contraindicated in females with acute hepatitis or severe (decompensated) cirrhosis of the liver. Discontinue ANNOVERA if jaundice develops. Acute liver test abnormalities may necessitate the discontinuation of ANNOVERA use until the liver tests return to normal and ANNOVERA causation has been excluded.

Liver Tumors

ANNOVERA is contraindicated in females with benign or malignant liver tumors. Hepatic adenomas are associated with CHC use (estimated 3.3 cases/100,000 CHC users). Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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

Stop ANNOVERA prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir. ANNOVERA can be restarted 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

**Hypertension**

ANNOVERA is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease. For all females, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop ANNOVERA if blood pressure rises significantly.

**Age-Related Considerations**

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Certain conditions, such as smoking and migraine headache without aura, that do not contraindicate CHC use in younger females, are contraindications to use in women over 35 years of age. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating ANNOVERA for women over 35 years, such as hypertension, diabetes, dyslipidemia, and obesity.

**Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Females with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

**Adverse Carbohydrate and Lipid Metabolic Effects**

Hyperglycemia

ANNOVERA is contraindicated in diabetic females over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of >20 years duration. ANNOVERA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are taking ANNOVERA.

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemia. ANNOVERA may cause adverse lipid changes. Females with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using ANNOVERA.

**Headache**

ANNOVERA is contraindicated in females with certain headaches. Evaluate new or significant changes in headaches, including migraines, and discontinue ANNOVERA if indicated.

**Bleeding Irregularities and Amenorrhea**

Females using ANNOVERA may experience unscheduled (breakthrough) bleeding and spotting, especially during the first month of use. If unscheduled bleeding occurs or persists, check for causes such as pregnancy or malignancy.

Based on subject diaries from the two clinical efficacy trials of ANNOVERA, 5–10% of females experienced unscheduled bleeding per 28-day cycle. A total of 41 subjects (1.7%) discontinued use due to menstrual disorders including metrorrhagia, menorrhagia, and abnormal withdrawal bleeding. Females who are not pregnant and use ANNOVERA may experience amenorrhea. Based on subject diary data from two clinical trials for up to 13 cycles, amenorrhea occurred in 3–5% of females per cycle using ANNOVERA and in 0.9% of females in all 13 cycles. If scheduled bleeding does not occur, consider the possibility of pregnancy.

**Depression**

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

**Cervical Cancer**

Some studies suggest that CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia.

**Effect on Binding Globulins**

The estrogen component of ANNOVERA may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

**Hereditary Angioedema**

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

**Chloasma**

Chloasma may occur with ANNOVERA use, especially in females with a history of chloasma gravidarum. Advise females who tend to develop chloasma to avoid exposure to the sun or ultraviolet radiation while using ANNOVERA.

**Toxic Shock Syndrome (TSS)**

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

**Vaginal Use**

Some females are aware of the vaginal system on occasion during the 21 days of use or during coitus, and partners may feel the vaginal system during coitus. ANNOVERA may not be suitable for females with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Vaginal and cervical erosion and/or ulceration has been reported in females using other contraceptive vaginal devices. In some cases, the ring adhered to vaginal tissue, which necessitated removal by a healthcare provider.

## ADVERSE REACTIONS

**Clinical Trial Experience**

Most Common Adverse Reactions

In clinical trials, adverse reactions reported in by ≥5% of ANNOVERA-treated subjects include: headache, including migraine (38.6%); nausea/vomiting (25.0%); vulvovaginal mycotic infection/vaginal candidiasis (14.5%); abdominal pain/lower/upper (13.3%); dysmenorrhea (12.5%); vaginal discharge (11.8%); UTI/cystitis/pyelonephritis/genitourinary tract infection (10.0%); breast pain/tenderness/discomfort (9.5%); metrorrhagia/menstrual disorder (7.5%); diarrhea (7.2%); and genital pruritus (5.5%).

Adverse Reactions Leading to Discontinuation

Among subjects using ANNOVERA for contraception, 12% discontinued from the clinical trials due to an adverse reaction. Adverse reactions leading to discontinuation by ≥1% of ANNOVERA-treated subjects, include: metrorrhagia/menorrhagia (1.7%); headache, including migraine (1.3%), vaginal discharge/vulvovaginal mycotic infections (1.3%); nausea/vomiting (1.2%). In addition, 1.4% of subjects discontinued ANNOVERA use due to vaginal system expulsions.

Serious Adverse Reactions

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

## DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of ANNOVERA or increase breakthrough bleeding. Counsel patients to use a backup or alternative method of contraception when enzyme inducers are used with ANNOVERA. Do not co-administer ANNOVERA with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Discontinue ANNOVERA if pregnancy occurs.

**Lactation**

Not recommended for nursing mothers; can decrease milk production.

**Pediatric Use**

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

**Geriatric Use**

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

**Hepatic Impairment**

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of ANNOVERA. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

**Renal Impairment**

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

**Body Mass Index (BMI)/Body Weight**

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

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*Source: Kantar Media, Medical Surgical Study June 2020, Obstetrics/Gynecology Combined Office & Hospital Readers.
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* A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

**References: 1.** Blatt AJ, et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015;123(5):282-288. doi:10.1002/ cncy.21544 (Study included ThinPrep, SurePath and Hybrid Capture 2 assay). **2.** Austin RM, et al. Enhanced detection of cervical cancer and precancer through use of imaged liquid-based cytology in routine cytology and HPV cotesting. Am J Obstet Gynecol. 2018;150(5):385-392. doi:10.1093/ajcp/aqy114 (Study included ThinPrep Pap test, ThinPrep imaging, Digene HPV, Cervista HPV and Aptima HPV).

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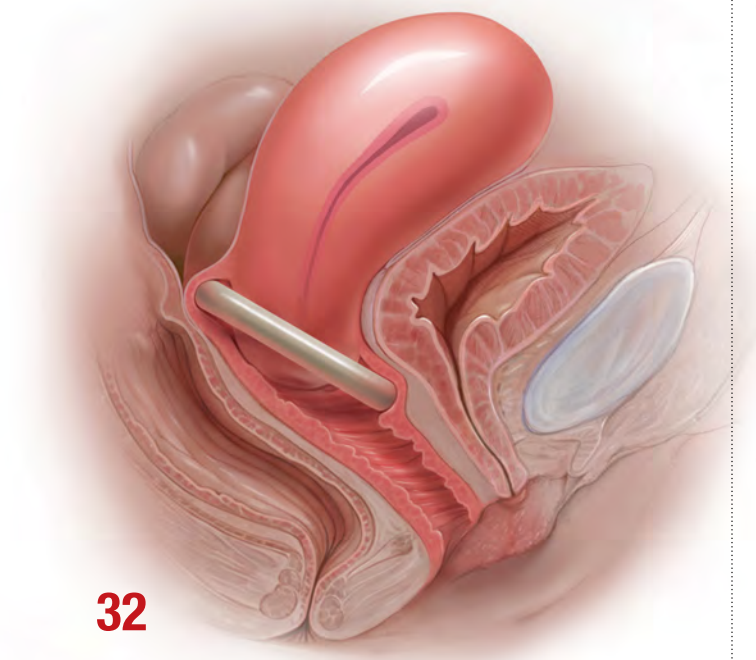



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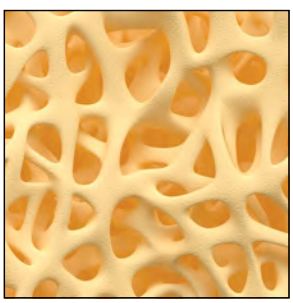

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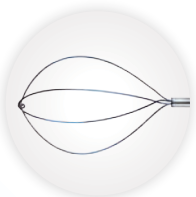

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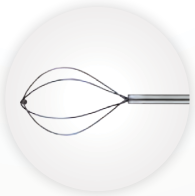

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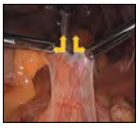

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**CHRISTINE E. FOLEY, MD, AND TED T. LEE, MD**

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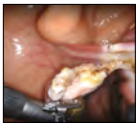

### Safety and efficiency in the laparoscopic hysterectomy: Techniques to optimize the surgical approach
**JACOB LAUER, MD, MPH; ARNOLD ADVINCULA, MD; AND JIN HEE KIM, MD**

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# For obese postmenopausal women, what options may decrease endometrial cancer risk?

Intentional weight loss, including diet, exercise, and bariatric surgery, as well as progestin treatment, may help this population of women reduce their risk of endometrial cancer

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Endometrial cancer is the most common gynecologic malignancy, with approximately 59,000 cases diagnosed annually,[1] and a lifetime risk of approximately 3.1% in the United States.[2] Type I endometrial cancer includes tumors with endometrioid histology that are grade 1 or 2. Type II endometrial cancer includes tumors that have grade 3 endometrioid or non-endometrioid histology, including serous, clear cell, mucinous, squamous transitional cell, mesonephric, and undifferentiated tumors.[3] Type I endometrial cancer is hormone sensitive, generally stimulated by estrogen and suppressed by progestins.

Endometrial cancer is diagnosed at a mean age of 63 years,[4] and only 15% of cases occur before age 50.[5] Women with an elevated body mass index (BMI) have a markedly increased risk of both Types I and II endometrial cancer (**TABLE**, page 10).[6] Hence, endometrial cancer is highly prevalent in obese postmenopausal women. For these women health interventions that may reduce the risk of developing endometrial cancer include dieting, physical activity, bariatric surgery, and progestin therapy.

*doi: 10.12788/obgm.0055*

## Educating patients is a priority

Many women do not know that postmenopausal bleeding is a sign of endometrial cancer. All postmenopausal women should be advised that if they develop vaginal bleeding they need to be evaluated by a clinician.[7] Women who are knowledgeable about the link between postmenopausal vaginal bleeding and endometrial cancer can be encouraged to share this information with their postmenopausal friends in order to reach more people with this important information. All obese postmenopausal women should be advised that weight loss and increased physical activity can reduce the risk of developing endometrial cancer.

## How weight loss and physical activity affect risk

Intentional weight loss has been reported to reduce the risk of endometrial cancer in postmenopausal women. As part of the Women's Health Initiative observational study, 36,794 postmenopausal women aged 50 to 79 years with a uterus had their body weight and height measured at entry into the study and after 3 years of follow-up.[8] During the 11 years following study entry, there were 566 incident cases of endometrial cancer. Compared with women who had a stable weight, intentional weight loss of ≥5% was associated with a 40% reduction in the risk of endometrial cancer (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.42–0.86). Compared with women who had a stable weight, women who had weight gain ≥10% had an increased risk of endometrial cancer (HR, 1.26; 95% CI, 1.00–1.57).

High levels of physical activity may be associated with a decreased risk of endometrial cancer. In one

**TABLE Association of BMI and risk for Type I and Type II endometrial cancer[6]**

| BMI, kg/m$^2$ | Type I endometrial cancer (OR) | Type II endometrial cancer (OR) |
|---|---|---|
| < 25 | 1.00 | 1.00 |
| 25 to < 30 | 1.45 | 1.16 |
| 30 to < 35 | 2.52 | 1.73 |
| 35 to < 40 | 4.45 | 2.15 |
| > 40 | 7.14 | 3.11 |

Abbreviations: BMI, body mass index; OR, odds ratio.

study, compared with a sedentary lifestyle, higher levels of physical activity were reported to be associated with a decreased risk of endometrial cancer.[9]

## How bariatric surgery affects risk

Many cancers are associated with obesity, including endometrial, breast, colon, pancreas, gallbladder, and renal. Obesity is associated with increased conversion of androgens to estrogens in fat tissue, stimulating excessive endometrial proliferation and increasing the risk of endometrial hyperplasia and cancer. Bariatric surgery reliably causes sustained weight reduction. Multiple studies have reported that bariatric surgery reduces the risk of endometrial cancer.

Schauer and colleagues used data from the Kaiser Permanente health system to identify 22,198 obese people who had undergone bariatric surgery and 66,427 matched controls who were obese but did not have surgery.[10] The study population was 81% female, with a mean age of 45 years and a mean BMI of 45 kg/m$^2$. After an average 3.5 years of follow-up there were 2,542 incident cases of cancer, including 322 cases of endometrial cancer. Compared with conventional weight loss treatment, bariatric surgery reduced the risk of endometrial cancer by 50% (HR, 0.50; 95% CI, 0.37–0.67; *P*<.001).[10] In addition, bariatric surgery reduced the risk of colon and pancreatic cancer by 41% and 54%, respectively.[10]

In the Swedish Obese Subjects (SOS) study, 1,420 women who underwent bariatric surgery and 1,447 matched controls who received conventional obesity treatment were followed for 18 years.[11] At study entry, the mean age of the women was approximately 48 years, and the mean BMI was approximately 42 kg/m$^2$. In follow-up there were 76 incident cases of endometrial cancer. Compared with women receiving conventional obesity treatment, women who had bariatric surgery had a non–statistically significant 49% decrease in the risk of developing endometrial cancer (HR, 0.51; 95% CI, 0.24–1.10)

In a systematic review of 5 additional studies (not including publications 10 or 11) of the impact of bariatric surgery on the risk of developing endometrial cancer, the surgery was associated with a 68% risk reduction (odds ratio [OR], 0.32; 95% CI, 0.16–0.63) compared with matched obese women that did not have surgery.[12]

Although there are no randomized prospective studies showing that bariatric surgery reduces the risk of endometrial cancer, the weight of the observation evidence is strong. In addition, bariatric surgery was reported to reduce all-cause mortality in the SOS study.[13] Hence, for obese postmenopausal women, if lifestyle changes do not result in sustained weight loss, bariatric surgery may be an optimal approach to improving health outcomes.

## Progestin treatment and endometrial cancer risk

Estrogen stimulates endometrial cell proliferation. Hence, unopposed chronic exposure to estrogen is a major risk factor for developing endometrial hyperplasia and cancer. Progestins block the proliferative effect of estrogen and cause cell differentiation, resulting in stromal decidualization. Progestins also reduce the concentration of estrogen and progesterone receptors and increase the activity of enzymes that convert estradiol to estrone, blocking estrogen-induced endometrial proliferation.[14]

In women with endometrial hyperplasia, progestins have been shown to be effective in resolving the hyperplasia in approximately 80% of cases. Both oral progestins and the 52-mg levonorgestrel-containing intrauterine device (LNG-IUD) have been reported to be effective in the treatment of endometrial hyperplasia. In a Cochrane systematic review

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and meta-analysis, the 52-mg LNG-IUD was reported to be somewhat more effective in resolving endometrial hyperplasia than cyclic oral progestins (89% vs 72%, respectively).[15]

Other studies have also reported that the 52 mg LNG-IUD was more effective than oral progestin therapy for women with complex atypical endometrial hyperplasia.[16] There are no large randomized clinical trials of progestin therapy on prevention for future development of endometrial cancer in obese postmenopausal women who have a normal endometrial histology. However, for an obese perimenopausal woman, insertion of a 52-mg LNG-IUD may help to minimize excessive uterine bleeding during the menopause transition and reduce the risk of developing endometrial hyperplasia during the early postmenopause.

## We can help our patients reduce their risk of endometrial cancer

Obese postmenopausal women are at increased risk for developing endometrial cancer. Gynecologists play an important role in the prevention and early detection of endometrial cancer. We can make a difference and improve the health of our obese peri- and postmenopausal women by recommending interventions that reduce the risk of endometrial cancer, thereby improving the health of our patients. ●

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


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# Lifting the restrictions on mifepristone during COVID-19: A step in the right direction

The FDA's Elements to Assure Safe Use restrictions mandate in-person distribution of mifepristone at health care facilities. This in-person signature process places women at unnecessary risk during the COVID-19 pandemic.

**Erika Wallace, MD; Kirsten Jorgensen, MD; and Megan L. Evans, MD, MPH**

Mifepristone is a safe, effective, and well-tolerated medication for managing miscarriage and for medical abortion when combined with misoprostol.[1,2] Since the US Food and Drug Administration (FDA) approved its use in 2000, more than 4 million women have used this medication.[3] The combination of mifepristone with misoprostol was used for 39% of all US abortions in 2017.[4] Approximately 10% of all clinically recognized pregnancies end in miscarriages, and many are safely managed with either misoprostol alone or with the combination of mifepristone and misoprostol.[5]

## The issue

The prescription and distribution of mifepristone is highly regulated by the FDA via requirements outlined in the Risk Evaluation and Mitigation Strategies (REMS) drug safety program. The FDA may determine a REMS is necessary for a specific drug to ensure the benefits of a drug outweigh the potential risks. A REMS may include an informative package insert for patients, follow-up communication to prescribers—including letters, safety protocols or recommended laboratory tests, or Elements to Assure Safe Use (ETASU). ETASU are types of REMS that are placed on medications that have significant potential for serious adverse effects, and without such restrictions FDA approval would be rescinded.

### Are mifepristone requirements fairly applied?

The 3 ETASU restrictions on the distribution of mifepristone are in-person dispensation, prescriber certification, and patient signatures on special forms.[6] The in-person dispensing requirement is applied to only 16 other medications (one of which is Mifeprex, the brand version of mifepristone), and Mifeprex/mifepristone are the only ones deemed safe for self-administration—meaning that patients receive the drug from a clinic but then may take it at a site of their choosing. The prescriber certification requirement places expectations on providers to account for distribution of doses and keep records of serial numbers (in effect, having clinicians act as both physician and pharmacist, as most medications are distributed and recorded in pharmacies). The patient form was recommended for elimination in 2016 due to its duplicative information and burden on patients—a recommendation that was then overruled by the FDA commissioner.[7]

These 3 requirements placed on mifepristone specifically target dosages for use related to abortions and miscarriages. Mifepristone is used to treat other medical conditions, with much higher doses, without the same restrictions—in fact, the FDA has allowed much higher doses of mifepristone to be mailed directly to a patient when prescribed for different disorders. The American College of Obstetricians and Gynecologists (ACOG) has long opposed the burdensome REMS requirements on mifepristone for reproductive health indications.[8]

Arguments regarding the safety of mifepristone must be understood in the context of how the medication is taken, and the unique difference with other medications that must be administered by physicians or in health care facilities. Mifepristone is self-administered, and the desired

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effect—evacuation of uterine contents—typically occurs after a patient takes the accompanying medication misoprostol, which is some 24 to 72 hours later. This timeframe makes it highly unlikely that any patient would be in the presence of their provider at the time of medication effect, thus an in-person dispensing requirement has no medical bearing on the outcome of the health of the patient.

### REMS changes during the COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic has necessarily changed the structure of REMS and ETASU requirements for many medications, with changes made in order to mitigate viral transmission through the limitation of unnecessary visits to clinics or hospitals. The FDA announced in March of 2020 that it would not enforce pre-prescription requirements, such as laboratory or magnetic resonance imaging results, for many medications (including those more toxic then mifepristone), and that it would lift the requirement for in-person dispensation of several medications.[9] Also in March 2020 the Department of Health and Human Services Secretary (HHS) and the Drug Enforcement Agency (DEA) activated a "telemedicine exception" to allow physicians to use telemedicine to satisfy mandatory requirements for prescribing controlled substances, including opioids.[10]

Despite repeated pleas from organizations, individuals, and physician groups, the FDA continued to enforce the REMS/ETASU for mifepristone as the pandemic decimated communities. Importantly, the pandemic has not had an equal effect on all communities, and the disparities highlighted in outcomes as related to COVID-19 are also reflected in disparities to access to reproductive choices.[11] By enforcing REMS/ETASU for mifepristone during a global pandemic, the FDA has placed additional burden on women and people who menstruate. As offices and clinics have closed, and as many jobs have evaporated, additional barriers have emerged, such as lack of childcare, fewer transportation options, and decreased clinic appointments.

As the pandemic continues to affect communities in the United States, ACOG has issued guidance recommending assessment for eligibility for medical abortion remotely, and has encouraged the use of telemedicine and other remote interactions for its members and patients to limit transmission of the virus.

## The lawsuit

On May 27, 2020, the American Civil Liberties Union (ACLU) (on behalf of ACOG, the Council of University Chairs of Obstetrics and Gynecology, New York State Academy of Family Physicians, SisterSong, and Honor MacNaughton, MD) filed a civil action against the FDA and HHS challenging the requirement for in-person dispensing of mifepristone and associated ETASU requirements during the COVID-19 pandemic. The plaintiffs sought this injunction based on the claim that these restrictions during the pandemic infringe on the constitutional rights to patients' privacy and liberty and to equal protection of the law as protected by the Due Process Clause of the Fifth Amendment. Additionally, the ACLU and other organizations said these unnecessary restrictions place patients, providers, and staff at unnecessary risk of viral exposure amidst a global pandemic.

## The verdict

On July 13, 2020, a federal court granted the preliminary injunction to suspend FDA's enforcement of the in-person requirements of mifepristone for abortion during the COVID-19 pandemic. The court denied the motion for suspension of in-person restrictions as applied to miscarriage management. The preliminary injunction applies nationwide without geographic limitation. It will remain in effect until the end of the litigation or for 30 days following the expiration of the public health emergency.

## What the outcome means

This injunction is a step in the right direction for patients and providers to allow for autonomy and clinical practice guided by clinician expertise. However, this ruling remains narrow. Patients must be counseled about mifepristone via telemedicine and sign a Patient Agreement Form, which must be returned electronically or by mail. Patients must receive a copy of the mifepristone medication guide, and dispensing of mifepristone must still be conducted by or under the supervision of a certified provider. The medication may not be dispensed by retail pharmacies, thus requiring providers to arrange for mailing of prescriptions to patients. Given state-based legal statutes regarding mailing of medications, this injunction may not lead to an immediate increase in access to care. In addition, patients seeking management for miscarriage must go to clinic to have mifepristone dispensed and thus risk exposure to viral transmission.

## What now?

The regulation of mifepristone—in spite of excellent safety and specifically for the narrow purpose of administration in the setting of

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

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

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

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

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

*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]

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# UPDATE Bone health

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A bone health expert considers recent evidence on osteosarcopenia as a risk factor, consequences of delayed denosumab dosing, bisphosphonates and atypical femur fracture, and the T-score as a treatment target in a romosozumab study

**IN THIS ARTICLE**



Increasingly, bone health and fragility fracture prevention is one of the most important aspects of healthy aging that we, as women's health care providers (HCPs), must be sure is part of our thought process in caring for women at midlife and beyond. Virtually all ObGyn HCPs are aware of breast health, both in terms of the clinical breast exam and imaging surveillance. The 5-year relative survival rate for "localized breast cancer" is 99%.[1] Most recent data on hip fracture, however, indicate that it is associated with a mortality in the first year of 21%![2] We need to be sure that our patients understand this.

Previously, this column provided an update on osteoporosis. In 2016, I asked to change the focus to "Update on bone health" to highlight that simply relying on dual energy x-ray absorptiometry (DXA) testing of bone mass with arbitrary cutoffs for osteoporosis, osteopenia, and normal bone mass is not adequate for improving overall bone health. The addition of the FRAX fracture risk assessment tool, now widely employed, as well as the trabecular bone score (TBS), not widely employed, helps to refine the assessment of patients' risk status. Further, issues such as sarcopenia, adequate dietary calcium and vitamin D supplementation, and fall prevention (improving balance, use of nonskid rugs in the bathroom, avoiding black ice when present, having nothing to slip on between the bed and the bathroom in the middle of the night, and so on) also are essential elements of "bone health."

Finally, I cannot stress enough the importance of developing a good relationship with whatever facility one uses for DXA testing in order to maximize use of the reports and potential limitations. In addition, we should identify a metabolic bone specialist for referral of unusual cases or patients who require medications unlikely to be prescribed by us as ObGyns, and develop some familiarity with therapies that may be utilized.

# Osteosarcopenia greatly enhances fall and fracture risk

*Sepúlveda-Loyola W, Phu S, Bani Hassan E, et al. The joint occurrence of osteoporosis and sarcopenia (osteosarcopenia): definitions and characteristics. J Am Med Dir Assoc. 2020;21:220-225.*

*Tokeshi S, Eguchi Y, Suzuki M, et al. Relationship between skeletal muscle mass, bone mineral density, and trabecular bone score in osteoporotic vertebral compression fractures. Asian Spine J. 2020 Sep 3. doi: 10.31616/asj.2020.0045.*

*Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers. J Cachexia Sarcopenia Muscle. 2020;11:609-618.*

The topic of sarcopenia as defined by the concurrent presence of low muscle mass, physical performance, and strength has been discussed previously in this Update series.[3] Now, osteosarcopenia, defined as the concomitant presence of osteoporosis or osteopenia combined with sarcopenia, seems to be an extremely important gauge of fracture risk, especially now as the population's longevity has increased dramatically. This new syndrome is associated with higher disability and rates of fracture and falls in older people compared with either entity (the bone component or the sarcopenia component) alone.[4,5] In fact, in the 2016 ICD-10-CM, sarcopenia was finally recognized as a disease entity.

Severe sarcopenia is known to increase the risk for falls.[6] Furthermore, evidence is increasing of cross talk between muscle and bone.[4] The diagnostic criteria of osteopenia and osteoporosis are well established; however, absolute criteria for sarcopenia lack an international consensus.

## Assess for osteopenia/osteoporosis plus sarcopenia to determine those at greatest fracture risk

Sepúlveda-Loyola and colleagues performed a cross-sectional analysis of 253 participants, of which 77% were women, average age 78, who presented for a "falls and fractures" risk assessment. T-scores were measured by DXA. In addition, the investigators measured components of sarcopenia, including physical performance (evaluated by hand grip strength, gait speed, timed up and go test, and 5-time sit to stand test) and dynamic and static balance. Falls in the previous year were self-reported, with 42% of participants having fallen once and 54%, more than once.

**Results.** Participants with osteosarcopenia had a statistically significant increased rate of falls of approximately threefold and an increased rate of fractures that was approximately fourfold when compared with osteopenia or osteoporosis alone.

Another important finding was that, despite the links between osteoporosis, fracture, and poor clinical outcomes, the investigators did not find differences in fracture rates in the osteopenic compared with the osteoporotic classifications. Their findings corroborated those of other studies that reported discrepancies in fractures and bone mineral density (BMD), with osteopenic older adults experiencing fracture rates similar to and in some cases greater than those diagnosed with osteoporosis.[7]

Thus, it appears that the use of T-scores that combine osteopenic and osteoporotic criteria into the osteosarcopenic category may be sufficient to capture individuals at the greatest risk of fracture.

## Skeletal muscle mass plays a role in vertebral compression fractures

Tokeshi and colleagues conducted retrospective observational study to investigate the relationships between skeletal muscle mass, BMD, and TBS in individuals with osteoporotic vertebral compression fractures.

They evaluated 142 patients with an average age of 75; of these, 30% had radiographically diagnosed vertebral compression

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

In the past, our assessment of risk for fragility fracture was based mostly on bone mass measurement by DXA. Scoring systems like the FRAX tool have included other risk factors, such as age, body mass index, previous fracture, family history of hip fracture, smoking, any history of rheumatoid arthritis, use of glucocorticoids, and alcohol consumption. However, sarcopenia is a condition characterized by loss of skeletal muscle mass, strength, and function. While it is a natural part of the aging process, when it is severe and coupled with osteopenia or osteoporosis, it significantly increases the risks of falls as well as fracture. Women's HCPs should increasingly think about the presence of sarcopenia in their patients, especially those with low bone mass (osteopenia *or* osteoporosis), particularly when making decisions about initiating pharmaceutical intervention. In addition, recommendations for resistive and balance exercises virtually should be universal.

fractures (average age, 79) and 70% had no vertebral compression fractures (average age, 70). Body composition was measured using whole-body DXA; appendicular skeletal muscle mass index was determined as the sum of upper and lower extremities' lean mass (kg/height in $m^2$). TBS was measured using the patented algorithm software on DXA scans for the lumbar vertebrae.

**Results.** The investigators found that the vertebral compression fracture group was statistically significantly older, had lower femur BMD, and had decreased leg muscle mass. The TBS was not identified as a risk factor.

**FAST TRACK**

*Clinicians should screen for osteosarcopenia via DXA imaging to quantitate bone mass, as is currently done, and, increasingly, quantify muscle mass*

## Certain lifestyle factors add to risk of osteosarcopenia

In an editorial, Kirk and colleagues summarized the epidemiology, diagnosis, and treatment of osteosarcopenia. They concluded that this syndrome can be expected to grow in age-related and disease-related states as a consequence of immunosenescence coinciding with an increase in sedentary lifestyle, obesity, and fat infiltration of muscle and bone.

Increasingly, clinicians should screen for osteosarcopenia via imaging methods (DXA) to quantitate bone mass (as is currently done) and, increasingly, quantify muscle mass. In addition, assessment of muscle strength, easily done by testing grip strength, as well as functional capacity (gait speed), will become increasingly important.

Finally, the authors call for a more comprehensive geriatric assessment that includes medical history and risk factors as well as treatment (including osteoporosis drugs, where indicated), and progressive resistance and balance exercises. Nutritional recommendations, in terms of protein, vitamin D, and calcium, also are necessary. They anticipate that diagnosis and treatment of osteosarcopenia will become part of routine health care in the future.

# The denosumab discontinuation dilemma

*Lyu H, Yoshida K, Zhao SS, et al. Delayed denosumab injections and fracture risk among patients with osteoporosis: a population-based cohort study. Ann Intern Med. 2020;173:516-526.*

*Tripto-Shkolnik L, Fund N, Rouach V, et al. Fracture incidence after denosumab discontinuation: real-world data from a large healthcare provider. Bone. 2020;130:115150.*

Denosumab, marketed under the brand name Prolia, is a human monoclonal antibody that blocks the binding of RANK ligand and inhibits development and activity of osteoclast, thus decreasing bone resorption and increasing BMD. In the original pivotal clinical trial of denosumab, almost 7,900 women between the ages of 60 and 90 (average age, 73) with osteoporotic T-scores were enrolled.[8] The women were randomly assigned to receive 60 mg of denosumab subcutaneously every 6 months or placebo for a

total of 3 years. In that trial, the denosumab-treated group, relative to the placebo group, showed a statistically significant decrease in radiographic vertebral fracture, hip fracture, and nonvertebral fracture.

An open-label extension study looked at denosumab use for a total of 10 years.[9] That study found that denosumab treatment for up to 10 years was associated with low rates of adverse events, low fracture incidence compared with that observed during the original trial, and continued increases in BMD without plateau. Thus, denosumab appeared to be an extremely safe and effective agent for treating postmenopausal women with osteoporosis.

## Denosumab cessation leads to rebound vertebral fractures

As opposed to bisphosphonates, denosumab does not incorporate into bone matrix, and bone turnover is not suppressed after cessation of its use. Reports have implied that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.[10] One theory is that unlike atypical femoral fractures that seem to emerge from failure of microdamage repair in cortical bone with long-term antiresorptive treatment, denosumab rebound–associated vertebral fractures seem to originate from the synergy of rapid bone resorption and accelerated microdamage accumulation in trabecular bone triggered by the discontinuation of this highly potent reversible agent.[11]

Post hoc analysis of the denosumab placebo-controlled trial and its extension reported that the vertebral fracture rate increased after denosumab discontinuation to the level observed in untreated patients.[12] Further, a majority of participants who did sustain vertebral fracture after discontinuing denosumab had multiple vertebral fractures, with the risk being greatest in participants who had a prior vertebral facture. This caused those authors to suggest that patients who discontinued denosumab should rapidly transition to an alternative antiresorptive treatment.

## Effect of dose delays, discontinuation on vertebral fracture rate

Lyu and colleagues recently described their population-based cohort study of the United Kingdom's Health Improvement Network primary care database between 2010 and 2019. They found that delayed administration of a subsequent denosumab dose by more than 16 weeks was associated with an increased risk for vertebral fracture compared with on-time dosing. They noted, however, that the evidence was insufficient to conclude that fracture risk at any other anatomic sites is increased with such a delay.

In a similar study, Tripto-Shkolnik and colleagues examined an Israeli database of 2.3 million members in a state-mandated health organization. They identified osteoporotic patients with at least 2 denosumab prescription dispenses and defined treatment discontinuation as a refill gap of 3 months or more. Fractures were identified by an osteoporosis registry, including fractures that occurred within 1 year from discontinuation in denosumab discontinuers as well as from the second year of treatment forward for persistent users. They identified 1,500 denosumab discontinuers (average age, 72) and 1,610 persistent users (average age also 72). At baseline, the groups were

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Denosumab is an extremely safe and effective treatment for postmenopausal osteoporosis. Discontinuation or even delay in dosing seems to result in a "rebound" effect of increased vertebral fractures and even multiple vertebral fractures, especially in those with history of a previous vertebral fracture. This is extremely important in this era of COVID-19, in which patients—especially elderly patients who are perceived to be at the greatest risk—often delay management of chronic disease to limit their potential exposure to the virus. Further, even in normal, nonpandemic times, clinicians need to make patients receiving denosumab aware of the importance of timely administration of doses as scheduled. If such dosing is not possible, then clinicians and patients need to be aware of the potential need for instituting other antiresorptive therapies. In addition, the need to ostensibly continue denosumab therapy for long periods of time and indefinitely may make it a less desirable choice for younger patients.

comparable in fracture history, smoking, and bone density.

In the discontinuation group, 0.8% had multiple vertebral fractures versus 0.1% in the persistent users ($P$ = .006); the overall rate of fractures per 100 patient-years of follow-up was 3 times higher in the discontinuation group than in the persistent user group, and the rate of vertebral fractures was almost 5 times higher in the discontinuation group.

# Atypical femur fracture risk and bisphosphonate use

*Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med. 2020;383:743-753.*

Since their introduction in the 1990s, bisphosphonates have been the mainstay of osteoporosis treatment. This category of medications inhibits osteoclast-mediated resorption and remodeling of bone. Various large, randomized, controlled trials have established the efficacy of bisphosphonates to increase BMD and decrease the risk of hip and vertebral fracture by as much as 40% to 70%.[13]

However, case reports of unusual fragility fractures in the subtrochanteric region and along the femoral diaphysis in patients treated with bisphosphonates started to appear approximately 15 years ago.[14] Since then, concerns and publicity about these atypical fractures have led to substantial declines in bisphosphonate use clinically.

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Many patients and even clinicians have moved away from the use of bisphosphonates to reduce fragility fracture risk because of fears of atypical femur fractures. With bisphosphonate use, the reduction in hip fracture as well as other fractures far overshadows the small but real complication of atypical femur fracture. The Asian population seems to have 4 to 6 times the risk for these atypical femur fractures. Thus, bisphosphonate therapy, especially now that it is available in generic formulations, should remain an important option for appropriate patients.

## Bisphosphonate preventive benefits versus atypical fracture risk

Black and colleagues reviewed data on women 50 years and older who were enrolled in the Kaiser Permanente health care system in California. The total cohort included slightly more than 1 million women, of which almost 200,000 (17.9%) used bisphosphonates at any point from 2007–2017.

A total of 277 atypical femur fractures occurred. Among bisphosphonate users, there were 1.74 fractures per 10,000 patient-years. Overall, there were almost 59 fractures per 10,000 person-years. The incidence of atypical fractures was highest in women between the ages of 75 and 84 years, and the incidence diminished after age 85. Rates of atypical fractures increased as the duration of bisphosphonate use increased. In addition, rates of atypical fractures decreased with time since bisphosphonate discontinuation.

The rate of atypical fractures in women who had never received bisphosphonate therapy was 0.1 per 10,000 person-years. The number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points along the 10 years of study. In White women, for instance, at 3 years there were 541 clinical fractures prevented and 149 hip fractures prevented, while 2 bisphosphonate-associated atypical fractures occurred, all per 10,000 women.

Interestingly, in the Asian population at the same time point, 330 clinical fractures were prevented and 91 hip fractures were prevented, but 8 atypical fractures of the femur

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occurred, per 10,000 women. The authors further referenced an earlier Kaiser study that showed that 49% of 142 atypical femur fractures occurred in Asian patients who comprised only 10% of the study population.[15]

The authors concluded that the risk of atypical femur fracture increases with longer duration of bisphosphate use and rapidly decreases after bisphosphate discontinuation. Asian women have a higher risk than White women. With bisphosphonate treatment, the absolute risk of atypical femur fracture is very low compared with the reduction in the risk of hip and other fractures.

# Romosozumab increases BMD gains and improves T-scores

*Cosman F, Lewiecki EM, Ebeling PR, et al. T-score as an indicator of fracture risk during treatment with romosozumab or alendronate in the ARCH trial. J Bone Miner Res. 2020;35:1333-1342*

**FAST TRACK**

*One year of romosozumab led to larger BMD gains than alendronate, and the T-score achieved with either therapy was directly related to subsequent fracture risk*

Romosozumab (Evenity) is a monoclonal antibody that binds and inhibits sclerostin, thus having the dual effect of increasing bone formation and decreasing bone resorption.[16] It is administered for 1 year as monthly doses of 210 mg subcutaneously. Previous studies have shown that romosozumab produces large increases in lumbar spine and total hip BMD,[17] reduces the risk of new vertebral and clinical fractures compared with placebo,[16] and reduces the risk of vertebral, clinical, nonvertebral, and hip fractures compared with alendronate over a median treatment period of 33 months (the ARCH study).[18]

According to the package insert, romosozumab is indicated "for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy."

## Should T-score be a therapeutic target?

Cosman and colleagues performed a post hoc analysis of the ARCH trial specifically to evaluate mean BMD and corresponding mean T-score changes (and the relationships between T-scores) after 1 year of romosozumab or alendronate therapy and subsequent fracture incidence. The study is quite detailed with much numerical data and statistical analysis.

Basically, the ARCH trial randomly assigned patients with osteoporosis to receive either monthly subcutaneous romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months. After the double-blind portion of the trial, all patients received open label weekly oral alendronate 70 mg through the end of study (24 months), although they were still blinded to the initial treatment assignment. In addition, patients received daily calcium and vitamin D supplements.

The data analysis found that 1 year of romosozumab led to larger BMD gains than alendronate therapy. Also, the T-score achieved with either therapy was directly related to subsequent fracture risk. The authors thus proposed that these data support the use of the T-score as a therapeutic target for patients with osteoporosis.

It is important to note that in the original ARCH study, the participants' average age was 71 years and approximately one-third were older than 75. The average T-score was -2.7 at both the lumbar spine and femoral neck. Approximately 20% of patients had a preexisting vertebral fracture, and approximately 20% had a previous nonvertebral fracture.

The authors of the current study, furthermore, found that mean BMD gains after 1 year of romosozumab treatment were more than twice those seen with alendronate

at the total hip, femoral neck, and lumbar spine. These BMD changes resulted in a larger proportion of patients who achieved T-scores above the osteoporosis level at each of the skeletal sites after 1 year of therapy. Fewer fractures occurred during the second year and the entire open label period among patients who had received romosozumab first compared with those who received alendronate. ●

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women's HCPs need to be aware of romosozumab even if they are not the ones primarily to prescribe it. Perhaps familiarity with the drug will allow some clinicians to begin to implement this treatment into their care for elderly patients with osteoporosis, especially those with pre-existing fractures. It may be useful to monitor patients' total hip T-score while on treatment if osteoporosis treatment goals have been achieved to minimize future fracture risk.


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## COMMENTARY

CONTINUED FROM PAGE 14

abortion and miscarriage care—is by definition a discriminatory practice against patients and providers. As clinicians, we are duty-bound to speak out against injustices to our practices and our patients. At a local level, we can work to implement safe practices in the setting of this injunction and continue to work on a national level to ensure this injunction becomes permanent and with more broad scope to eliminate all of the REMS requirements for mifepristone.

### Action items

- Act locally! Are you an abortion provider? Contact your local ACLU or lawyer in your area for assistance navigating the legal landscape to prescribe after this injunction.
- Act statewide! Press candidates in your state to stand up for science and data. Support legislative acts and bills that address combating discriminatory regulations.
- Act nationally! The President is responsible for appointing the Commissioner of the FDA and the Secretary of Health and Human Services (with Senate advice and consent). Who we elect matters. Seek out opportunities to become involved in increasing access to and awareness of voter registration and Election Day, and speak out against voter suppression. Make sure you are always registered to vote and check your area to review new recommendations amidst the pandemic. ●

# The pill toolbox: How to choose a combined oral contraceptive

A thorough understanding of the risks and benefits, including noncontraceptive advantages, of varied COC formulations strengthens your pill armamentarium and aids patient decision making

**Charlotte M. Page, MD**

**IN THIS ARTICLE**



In the era of long-acting reversible contraceptives (LARCs), the pill can seem obsolete. However, it is still the second most commonly used birth control method in the United States, chosen by 19% of female contraceptive users as of 2015–2017.[1] It also has noncontraceptive benefits, so it is important that obstetrician-gynecologists are well-versed in its uses. In this article, I will focus on combined oral contraceptives (COCs; **TABLE 1**, page 27), reviewing the major risks, benefits, and adverse effects of COCs before focusing on recommendations for particular formulations of COCs for various patient populations.

## Benefits and risks

There are numerous noncontraceptive benefits of COCs, including menstrual cycle regulation; reduced risk of ovarian, endometrial, and colorectal cancer; and treatment of menorrhagia, dysmenorrhea, acne, menstrual migraine, premenstrual syndrome and premenstrual dysphoric disorder, pelvic pain due to endometriosis, and hirsutism.

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### Common patient concerns

In terms of adverse effects, there are more potential unwanted effects of concern to women than there are ones validated in the literature. Accepted adverse effects include nausea, breast tenderness, and decreased libido. However, one of the most common concerns voiced during contraceptive counseling is that COCs will cause weight gain. A 2014 Cochrane review identified 49 trials studying the weight gain question.[2] Of those, only 4 had a placebo or nonintervention group. Of these 4, there was no significant difference in weight change between the COC-receiving group and the control group. When patients bring up their concerns, it may help to remind them that women tend to gain weight over time whether or not they are taking a COC.

Another common concern is that COCs cause mood changes. A 2016 review by Schaffir and colleagues sheds some light on this topic,[3] albeit limited by the paucity of prospective studies. This review identified only 1 randomized controlled trial comparing depression incidence among women initiating a COC versus a placebo. There was no difference in the incidence of depression among the groups at 3 months. Among 4 large retrospective studies of women using COCs, the agents either had no or a beneficial effect on mood. Schaffir's review reports that there may be greater mood adverse effects with COCs among women with underlying mood disorders.

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**54%** **OPIOID-SPARED*** Women took ≤10 mg of oxycodone with no bother or stress from ORAEs through 72 hours (*P*=0.0012).[1§]

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ORAEs=opioid-related adverse events (such as vomiting, itching, sweating, freezing, and dizziness).
†The clinical benefit of the decrease in opioid consumption was not demonstrated in the pivotal trials.
†A prospective, multicenter, randomized, double-blind clinical trial of 186 patients who underwent an elective C-section with a multimodal pain management protocol, including a transversus abdominis plane (TAP) block using either 20 mL EXPAREL 266 mg, 20 mL 0.25% bupivacaine HCl, and 20 mL normal saline for a total volume of 60 mL (30 mL volume on each side); or 20 mL 0.25% bupivacaine HCl and 40 mL normal saline for a total volume of 60 mL (30 mL volume on each side).[1]
‡Single-center retrospective chart review of 201 patients ≥18 years of age who underwent C-section with either a multimodal pain management protocol including a TAP block with 20 mL EXPAREL 266 mg, 30 mL 0.25% bupivacaine HCl, and 30 mL normal saline for a total volume of 80 mL (40 mL volume on each side); or a multimodal pain management protocol alone. Mean hospital length of stay was 2.9 days with EXPAREL (n=97) vs 3.9 days without EXPAREL (n=89). Time to ambulation was 18.7 hours with EXPAREL (n=67) and 30.7 hours without EXPAREL (n=60).[2]
§Defined as patients who took no more than 10 mg of oxycodone (15 mg of morphine or equivalent) with no bother or stress from vomiting, itching, sweating, freezing, or dizziness through 72 hours.

**Indication**

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

**Important Safety Information**

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation. If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine. EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.

**Warnings and Precautions Specific to EXPAREL**

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL. EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks **other than interscalene brachial plexus nerve block**, or intravascular or intra-articular use. The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.

**Warnings and Precautions for Bupivacaine-Containing Products**

**Central Nervous System (CNS) Reactions:** There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression. **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death. **Allergic Reactions:** Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use. **Methemoglobinemia:** Cases of methemoglobinemia have been reported with local anesthetic use.

**Please refer to brief summary of Prescribing Information on adjacent page.**

**For more information, please visit www.EXPAREL.com or call 1-855-793-9727.**

**References: 1.** Nedeljkovic SS, Kett A, Vallejo MC, et al. Transversus abdominis plane block with liposomal bupivacaine for pain after cesarean delivery in a multicenter, randomized, double-blind, controlled trial. *Anesth Analg*. doi: 10.1213/ANE.0000000000005075. [Epub ahead of print]. **2.** Baker BW, Villadiego LG, Lake YN, et al. Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. *J Pain Res*. 2018;11:3109-3116.

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**Brief Summary**
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**INDICATIONS AND USAGE**

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

Limitation of Use: Safety and efficacy has not been established in other nerve blocks.

**CONTRAINDICATIONS**

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

**WARNINGS AND PRECAUTIONS**

**Warnings and Precautions Specific for EXPAREL**

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks other than interscalene brachial plexus nerve block
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups.

- patients younger than 18 years old
- pregnant patients

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days as seen in clinical trials.

**ADVERSE REACTIONS**

**Clinical Trial Experience**

Adverse Reactions Reported in Local Infiltration Clinical Studies

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting. The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

Adverse Reactions Reported in Nerve Block Clinical Studies

The safety of EXPAREL was evaluated in four randomized, double-blind, placebo-controlled nerve block clinical studies involving 469 patients undergoing various surgical procedures. Patients were administered a dose of either 133 or 266 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, pyrexia, and constipation.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration as a nerve block were muscle twitching, dysgeusia, urinary retention, fatigue, headache, confusional state, hypotension, hypertension, hypoesthesia oral, pruritus generalized, hyperhidrosis, tachycardia, sinus tachycardia, anxiety, fall, body temperature increased, edema peripheral, sensory loss, hepatic enzyme increased, hiccups, hypoxia, post-procedural hematoma.

Postmarketing Experience

These adverse reactions are consistent with those observed in clinical studies and most commonly involve the following system organ classes (SOCs): Injury, Poisoning, and Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy, pain), Skin and Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest).

**DRUG INTERACTIONS**

The toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity. Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

Patients who are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

**Examples of Drugs Associated with Methemoglobinemia:**

| Class | Examples |
|---|---|
| Nitrates/Nitrites | nitric oxide, nitroglycerin, nitroprusside, nitrous oxide |
| Local anesthetics | articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine |
| Antineoplastic agents | cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase |
| Antibiotics | dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides |
| Antimalarials | chloroquine, primaquine |
| Anticonvulsants | Phenobarbital, phenytoin, sodium valproate |
| Other drugs | acetaminophen, metoclopramide, quinine, sulfasalazine |

Bupivacaine

Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

Non-bupivacaine Local Anesthetics

EXPAREL should not be admixed with local anesthetics other than bupivacaine. Nonbupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. There are no data to support administration of other local anesthetics prior to administration of EXPAREL.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

Water and Hypotonic Agents

Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose equivalent to 1.6 times the maximum recommended human dose (MRHD) of 266 mg. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.5 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risks to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Clinical Considerations

Labor or Delivery

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia. While EXPAREL has not been studied with this technique, the use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death.

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Data

Animal Data

Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard plate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) and rabbit doses were 1.3, 5.8, and 22.2 mg/kg/day (equivalent to 0.1, 0.4 and 1.6 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Decreased pup survival was noted at 1.5 times the MRHD in a rat pre- and post-natal development study when pregnant animals were administered subcutaneous doses of 4.4, 13.3, and 40 mg/kg/day buprenorphine hydrochloride (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) from implantation through weaning (during pregnancy and lactation).

**Lactation**

Risk Summary

Limited published literature reports that bupivacaine and its metabolite, pipecoloxylidide, are present in human milk at low levels. There is no available information on effects of the drug in the breastfed infant or effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXPAREL and any potential adverse effects on the breastfed infant from EXPAREL or from the underlying maternal condition.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the total number of patients in the EXPAREL local infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. Of the total number of patients in the EXPAREL nerve block clinical studies (N=531), 241 patients were greater than or equal to 65 years of age and 60 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Impairment**

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease.

**Renal Impairment**

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. This should be considered when performing dose selection of EXPAREL.

**OVERDOSAGE**

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution.

Signs and symptoms of overdose include CNS symptoms (perioral paresthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia and asystole).

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,500 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Management of Local Anesthetic Overdose

At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, maybe indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

**DOSAGE AND ADMINISTRATION**

**Important Dosage and Administration Information**

- EXPAREL is intended for single-dose administration only.
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL.
- DO NOT dilute EXPAREL with water for injection or other hypotonic agents, as it will result in disruption of the liposomal particles.
- Use suspensions of EXPAREL diluted with preservative-free normal (0.9%) saline for injection or lactated Ringer's solution within 4 hours of preparation in a syringe.
- Do not administer EXPAREL if it is suspected that the vial has been frozen or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- Inspect EXPAREL visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer EXPAREL if the product is discolored.

**Recommended Dosing in Adults**

Local Analgesia via Infiltration

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266mg (20 mL), and is based on the following factors:

- Size of the surgical site
- Volume required to cover the area
- Individual patient factors that may impact the safety of an amide local anesthetic

As general guidance in selecting the proper dosing, two examples of infiltration dosing are provided:

- In patients undergoing bunionectomy, a total of 106 mg (8 mL) of EXPAREL was administered with 7 mL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.
- In patients undergoing hemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL), and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair.

**Compatibility Considerations**

Admixing EXPAREL with drugs other than bupivacaine HCl prior to administration is not recommended.

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

  The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

**Non-Interchangeability with Other Formulations of Bupivacaine**

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Administration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after interscalene brachial plexus nerve block. In general, peripheral nerve blocks have shown systemic plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

**PATIENT COUNSELING**

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

PACIRA PHARMACEUTICALS, INC.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

6,132,766 5,891,467 5,766,627 8,182,835



**For additional information call 1-855-RX-EXPAREL (1-855-793-9727)**

**Rx only** **November 2018**

CONTINUED FROM PAGE 24

**TABLE 1 Common brand names of combined oral contraceptives and their components**

| Brand name | Progestin (mg) | Estrogen (µg) | Cycle |
|---|---|---|---|
| Yaz | Drospirenone (3) | Ethinyl estradiol (20) | 24/4 |
| Yasmin | Drospirenone (3) | Ethinyl estradiol (30) | 21/7 |
| Amethyst | Levonorgestrel (0.09) | Ethinyl estradiol (20) | No placebo pills; can be used continuously |
| Loestrin Fe 1/20<br>Junel Fe 1/20 | Norethindrone (1) | Ethinyl estradiol (20) | 21/7 ferrous fumarate instead of placebo |
| Loestrin 1.5/30<br>Junel 1.5/30 | Norethindrone (1.5) | Ethinyl estradiol (30) | 21/7. Also available with ferrous fumarate. |
| Sprintec<br>Ortho-Cyclen | Norgestimate (0.25) | Ethinyl estradiol (35) | 21/7 |
| Lo Loestrin Fe | Norethindrone (1, 0) | Ethinyl estradiol (10, 10) | 24/2/2 ferrous fumarate (biphasic) |
| Ortho Tri-Cyclen<br>Tri-Sprintec | Norgestimate (0.18, 0.215, 0.25) | Ethinyl estradiol (35, 35, 35) | 7/7/7/7 (triphasic) |
| Seasonique | Levonorgestrel (0.15, 0) | Ethinyl estradiol (30, 10) | 84/7 (no true placebo pill) |
| LoSeasonique | Levonorgestrel (0.1, 0) | Ethinyl estradiol (20, 10) | 84/7 (no true placebo pill) |
| Introvale | Levonorgestrel (0.15) | Ethinyl estradiol (30) | 84/7 |

Patients may worry that COC use will permanently impair their fertility or delay return to fertility after discontinuation. Research does indicate that return of fertility after stopping COCs often takes several months (compared with immediate fertility after discontinuing a barrier method). However, there still seem to be comparable conception rates within 12 months after discontinuing COCs as there are after discontinuing other common nonhormonal or hormonal contraceptive methods. Fertility is not impacted by the duration of COC use. In addition, return to fertility seems to be comparable after discontinuation of extended cycle or continuous COCs compared with traditional-cycle COCs.[4]

## COC safety

Known major risks of COCs include venous thromboembolism (VTE). The risk of VTE is about double among COC users than among nonpregnant nonusers: 3–9 per 10,000 woman-years compared with 1–5.[5] In a study by the US Food and Drug Administration, drospirenone-containing COCs had double the risk of VTE than other COCs. However, the position of the American College of Obstetricians and Gynecologists on this increased risk of VTE with drospirenone-containing pills is that it is "possible" and "minimal."[5] It is important to remember that an alternative to COC use is pregnancy, in which the VTE risk is about double that among COC users, at 5–20 per 10,000 woman-years. This risk increases further in the postpartum period, to 40–65 per 10,000 woman-years.[5]

Another known major risk of COCs is arterial embolic disease, including cerebrovascular accidents and myocardial infarctions. Women at increased risk for these complications include those with hypertension, diabetes, and/or obesity and women who are aged 35 or older and smoke. Interestingly, women with migraines with aura are at increased risk for stroke but not for myocardial infarction. These women increase their risk of stroke 2- to 4-fold if they use COCs.

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## Different pills for different problems

With so many pills on the market, it is important for clinicians to know how to choose a particular pill for a particular patient. The following discussion assumes that the patient in question desires a COC for contraception, then offers guidance on how to choose a pill with patient-specific noncontraceptive benefits (**TABLE 2**).

**When HMB is a concern.** Patients with heavy menstrual bleeding may experience fewer bleeding and/or spotting days with extended cyclic or continuous use of a COC rather than with traditional cyclic use.[6] Examples of such COC options include:

- Introvale and Seasonique, both extended-cycle formulations
- Amethyst, which is formulated without placebo pills so that it can be used continuously
- any other COC prescribed with instructions for the patient to skip placebo pills.

An extrapolated benefit to extended-cycle or continuous COCs use for heavy menstrual bleeding is addressing anemia.

**For premenstrual dysphoric disorder,** the only randomized controlled trials showing improvement involve drospirenone-ethinyl estradiol pills (Yaz and Yasmin).[7] There is also evidence that extended cyclic or continuous use of these formulations is more impactful for premenstrual dysphoric disorder than a traditional cycle.[8]

**Keeping migraine avoidance and prevention in mind.** Various studies have looked at the impact of different COC formulations on menstrual-related symptoms. There is evidence of greater improvement in headache, bloating, and dysmenorrhea with extended cyclic or continuous use compared with traditional cyclic use.[6]

In terms of headache, let us delve into menstrual migraine in particular. Menstrual migraines occur sometime between 2 days prior to 2 days after the first day of menses and are linked to a sharp drop in estrogen levels. COCs are contraindicated in women with menstrual migraines with aura because of the increased stroke risk. For women with menstrual migraines *without* aura, COCs can prevent migraines. Prevention depends on minimizing fluctuations in estrogen levels; any change in estrogen level greater than 10 µg of ethinyl estradiol may trigger an estrogen-related migraine. All currently available regimens of COCs that comprise 21 days of active pills and 7 days of placebo involve a drop of more than 10 µg. Options that involve a drop of 10 µg or less include any continuous formulation, the extended formulation LoSeasonique (levonorgestrel 0.1 mg and ethinyl estradiol 20 µg for 84 days, then ethinyl estradiol 10 µg for 7 days), and Lo Loestrin (ethinyl estradiol 10 µg and norethindrone 1 mg for 24 days, then ethinyl estradiol 10 µg for 2 days, then placebo for 2 days).[9]

**What's best for acne-prone patients?** All COCs should improve acne by increasing levels of sex hormone binding globulin. However, some comparative studies have shown drospirenone-containing COCs to be the most effective for acne. This finding makes sense in light of studies demonstrating antiandrogenic effects of drospirenone.[10]

**Managing PCOS symptoms.** It seems logical, by extension, that drospirenone-containing COCs would be particularly beneficial for treating hirsutism associated with polycystic ovary syndrome (PCOS). Other low-androgenic-potential progestins, such as a third-generation progestin (norgestimate or desogestrel), might similarly be hypothesized to be advantageous. However, there is currently insufficient evidence to recommend any one COC formulation over another for the indication of PCOS.[11]

**Ovarian cysts: Can COCs be helpful?** COCs are commonly prescribed by gynecologists for patients with functional ovarian cysts. It is important to note that COCs have not been found to hasten the resolution of existing cysts, so they should not be used for this purpose.[12] Studies of early COCs, which had high doses of estrogen (on the order of 50 µg), showed lower rates of cysts among users. This effect seems to be attenuated with the lower-estrogen-dose pills that are currently available, but there still appears to be benefit. Therefore, for a patient prone to cysts who desires an oral contraceptive, a COC containing estrogen 35 µg is likely to be the most beneficial of COCs currently on the market.[13,14]

**FAST TRACK**

*For women with menstrual migraines without aura, any continuous formulation COC or the extended formulations LoSeasonique or Lo Loestrin can help prevent migraine*

**TABLE 2 Recommended combined oral contraceptives for different patient problems**

| Problem | Recommended pill type | Pill examples |
|---|---|---|
| Menstrual migraine | Pill with 10 µg or less drop in ethinyl estradiol | LoSeasonique, Lo Loestrin |
| Headache, bloating, and dysmenorrhea | Extended cyclic or continuous | Seasonique, Introvale, Amethyst |
| Acne | Drospirenone-ethinyl estradiol | Yaz, Yasmin |
| Premenstrual dysphoric disorder | Drospirenone-ethinyl estradiol | Yaz, Yasmin |
| Polycystic ovary syndrome | Insufficient evidence to recommend one | |
| Functional ovarian cysts | Pill with ethinyl estradiol 35 µg | Sprintec, Ortho-Cyclen |
| Heavy menstrual bleeding | Extended cyclic or continuous | Seasonique, Introvale, Amethyst |
| Perimenopause | Extended cyclic or continuous pill with lower estrogen dose | Amethyst |
| Concurrent use of enzyme-inducing antiepileptic drug | Pill with ethinyl estradiol 50 µg | Kelnor, Ogestrel |
| Concurrent use of lamotrigine in particular | Continuous pill with ethinyl estradiol 50 µg | Kelnor, Ogestrel in continuous fashion |

**TABLE 3 Recommended combined oral contraceptives to minimize adverse effects or risks**

| Adverse effect/risk | Recommended pill type | Pill examples |
|---|---|---|
| Mood changes | Extended cyclic or continuous | Seasonique, Introvale, Amethyst |
| Nausea, breast tenderness | Pill with ethinyl estradiol 20 µg or lower | Loestrin 1/20, Lo Loestrin |
| Hypertension | Drospirenone-ethinyl estradiol | Yaz, Yasmin |
| Intermenstrual bleeding | Third-generation progestin with more than 20 µg ethinyl estradiol | Sprintec, Ortho-Cyclen |
| Venous thromboembolism | First- or second-generation progestin with low estrogen dose | Loestrin 1/20, Amethyst |
| Weight gain | Drospirenone-ethinyl estradiol | Yaz, Yasmin |

**Lower-dosage COCs in perimenopause may be beneficial.** COCs can ameliorate perimenopausal symptoms including abnormal uterine bleeding and vasomotor symptoms. Clinicians are often hesitant to prescribe COCs for perimenopausal women because of increased risk of VTE, stroke, myocardial infarction, and breast cancer with increasing age. However, age alone is not a contraindication to any contraceptive method. An extended cyclic or continuous regimen COC may be the best choice for a perimenopausal woman in order to avoid vasomotor symptoms that occur during hormone-free intervals. In addition, given the increasing risk of adverse effects like VTE with estrogen dose, a lower estrogen formulation is advisable.[15]

**Patients with epilepsy** who are taking antiepileptic drugs (AEDs) are a special population when it comes to COCs. Certain AEDs induce hepatic enzymes involved in the metabolism and protein binding of

COCs, which can result in contraceptive failure. Strong inducers are carbamazepine, oxcarbazepine, perampanel, phenobarbital, phenytoin, and primidone. Weak inducers are clobazam, eslicarbazepine, felbamate, lamotrigine, rufinamide, and topiramate. Women taking any of the above AEDs are recommended to choose a different form of contraception than a COC. However, if they are limited to COCs for some reason, a preparation containing estrogen 50 µg is recommended. It is speculated that the efficacy and adverse effects of COCs with increased hormone doses, used in combination with enzyme-inducing AEDs, should be comparable to those with standard doses when not combined with AEDs; however, this speculation is unproven.[16] There are few COCs on the market with estrogen doses of 50 µg, but a couple of examples are Kelnor and Ogestrel.

Additional factors have to be considered with concurrent COC use with the AED lamotrigine since COCs increase clearance of this agent. Therefore, patients taking lamotrigine who start COCs will need an increase in lamotrigine dose. To avoid fluctuations in lamotrigine serum levels, use of a continuous COC is recommended.[17]

**FAST TRACK**

*For obese women who are high risk for VTE but medically appropriate for a COC, the best options are a first- or second-generation progestin combined with a low-dose estrogen*

## Pill types to minimize adverse effects or risks

For women who desire to use a COC for contraception but who are at risk for a particular complication or are bothered by a particular adverse effect, ObGyns can optimize the choice of pill (**TABLE 3**, page 29). For example, women who have adverse effects of nausea and/or breast tenderness may benefit from reducing the estrogen dose to 20 µg or lower.[18]

### Considering VTE

As discussed previously, VTE is a risk with all COCs, but some pills confer greater risk than others. For one, VTE risk increases with estrogen dose. In addition, VTE risk depends on the type of progestin. Drospirenone and third-generation progestins (norgestimate, gestodene, and desogestrel) confer a higher risk of VTE than first- or second-generation progestins. For example, a pill with estradiol 30 µg and either a third-generation progestin or drospirenone has a 50% to 80% higher risk of VTE compared with a pill with estradiol 30 µg and levonorgestrel.

For patients at particularly high risk for VTE, COCs are contraindicated. For patients for whom COCs are considered medically appropriate but who are at higher risk (eg, obese women), it is wise to use a pill containing a first-generation (norethindrone) or second-generation progestin (levonorgestrel) combined with the lowest dose of estrogen that has tolerable adverse effects.[19]

### What about hypertension concerns?

Let us turn our attention briefly to hypertension and its relation to COC use. While the American College of Cardiology and the American Heart Association redefined hypertension in 2017 using a threshold of 130/80 mm Hg, the American College of Obstetricians and Gynecologists (ACOG) considers hypertension to be 140/90 mm Hg in terms of safety of using COCs. ACOG states, "women with blood pressure below 140/90 mm Hg may use any hormonal contraceptive method."[20] In women with hypertension in the range of 140-159 mm Hg systolic or 90-99 mm Hg diastolic, COCs are category 3 according to the US Medical Eligibility Criteria for Contraceptive Use, meaning that the risks usually outweigh the benefits. For women with blood pressures of 160/110 mm Hg or greater, COCs are category 4 (contraindicated). If a woman with mild hypertension is started on a COC, a drospirenone-containing pill may be the best choice because of its diuretic effects. While other contemporary COCs have been associated with a mild increase in blood pressure, drospirenone-containing pills have not shown this association.[21]

### At issue: Break-through bleeding, mood, and weight gain

For women bothered by intermenstrual bleeding, use of a COC with a third-generation progestin may be preferable to use of one with a first- or second-generation. It may be because of decreased abnormal bleeding that COCs with third-generation progestins have lower

discontinuation rates.[22] In addition, COCs containing estrogen 20 µg or less are associated with more intermenstrual bleeding than those with more than 20 µg estrogen.[23] Keep in mind that it is common with any COC to have intermenstrual bleeding for the first several months.

For women with pre-existing mood disorders or who report mood changes with COCs, it appears that fluctuations in hormone levels are problematic. Consistently, there is evidence that monophasic pills are preferable to multiphasic and that extended cyclic or continuous use is preferable to traditional cyclic use for mitigating mood adverse effects. There is mixed evidence on whether a low dose of ethinyl estradiol is better for mood.[3]

Although it is discussed above that randomized controlled trials have not shown an association between COC use and weight gain, many women remain concerned. For these women, a drospirenone-containing COC may be the best choice. Drospirenone has antimineralocorticoid activity, so it may help prevent water retention.

**A brief word about multiphasic COCs.** While these pills were designed to mimic physiologic hormone fluctuations and minimize hormonal adverse effects, there is insufficient evidence to compare their effects to those of monophasic pills.[24] Without such evidence, there is little reason to recommend a multiphasic pill to a patient over the more straightforward monophasic formulation.

## Conclusion

There are more nuances to prescribing an optimal COC for a patient than may initially come to mind. It is useful to remember that any formulation of pill may be prescribed in an extended or continuous fashion, and there are benefits for such use for premenstrual dysphoric disorder, heavy menstrual bleeding, perimenopause, and menstrual symptoms. Although there are numerous brands of COCs available, a small cadre will suffice for almost all purposes. Such a "toolbox" of pills could include a pill formatted for continuous use (Seasonique), a low estrogen pill (Loestrin), a drospirenone-containing pill (Yaz), and a pill containing a third-generation progestin and a higher dose of estrogen (Sprintec). ●


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PART 1

# Pessaries for POP and SUI: Your options and guidance on use

Gynecologists may not always "think pessary first" when it comes to pelvic organ prolapse management. However, it is important to be familiar with the array of available pessary options and how to select a device based on the patient's disorder and needs.

**Henry M. Lerner, MD**

**IN THIS ARTICLE**



Over the last 30 years, surgical correction of the common condition pelvic organ prolapse (POP) and stress urinary incontinence (SUI) has become so routine and straightforward that many gynecologists and urogynecologists choose surgery as their first choice for treating these conditions, withholding it only from the riskiest patients or from those who, for a variety of reasons, do not choose surgery. Moreover, as generalist gynecologists increasingly refer patients with POP or incontinence to their urogynecologist colleagues, they increasingly lack the skills, or have not been trained, to use conservative treatment strategies for these disorders. Thus, pessaries—devices constructed of inert plastic, silicone, or latex and placed inside the vagina to support prolapsed pelvic structures—frequently are not part of the general gynecologist's armamentarium.

When properly selected, however, pessaries used for indicated purposes and correctly fitted are an excellent, inexpensive, low-risk, and noninvasive tool that can provide immediate relief not only of POP but also of SUI and defecatory difficulties. As an alternative to surgery, pessaries are especially valuable, because the other major nonsurgical modality for treatment of POP and incontinence—pelvic floor muscle training—often is not covered by insurance (making it expensive for patients), takes many weekly sessions to complete (which can make access challenging), and frequently is not readily available.[1]

POP is very common. An estimated 15% to 30% of women in North America have some degree of prolapse, and more than 500,000 surgeries for this condition are performed in the United States each year.[2] Risk factors for POP include:

- vaginal childbirth, especially higher parity
- advancing age
- high body mass index (BMI)
- prior hysterectomy
- raised intra-abdominal pressure, such as from obesity, chronic cough, or heavy lifting.

In addition to the discomfort caused by the herniation of pelvic and vaginal structures, POP also is associated with urinary incontinence (73%), urinary urgency and frequency (86%), and fecal incontinence (31%).[3]

Moreover, according to the US Census Bureau, the number of American women aged 65 or older will double to more than 40 million by 2030.[4] This will greatly increase the

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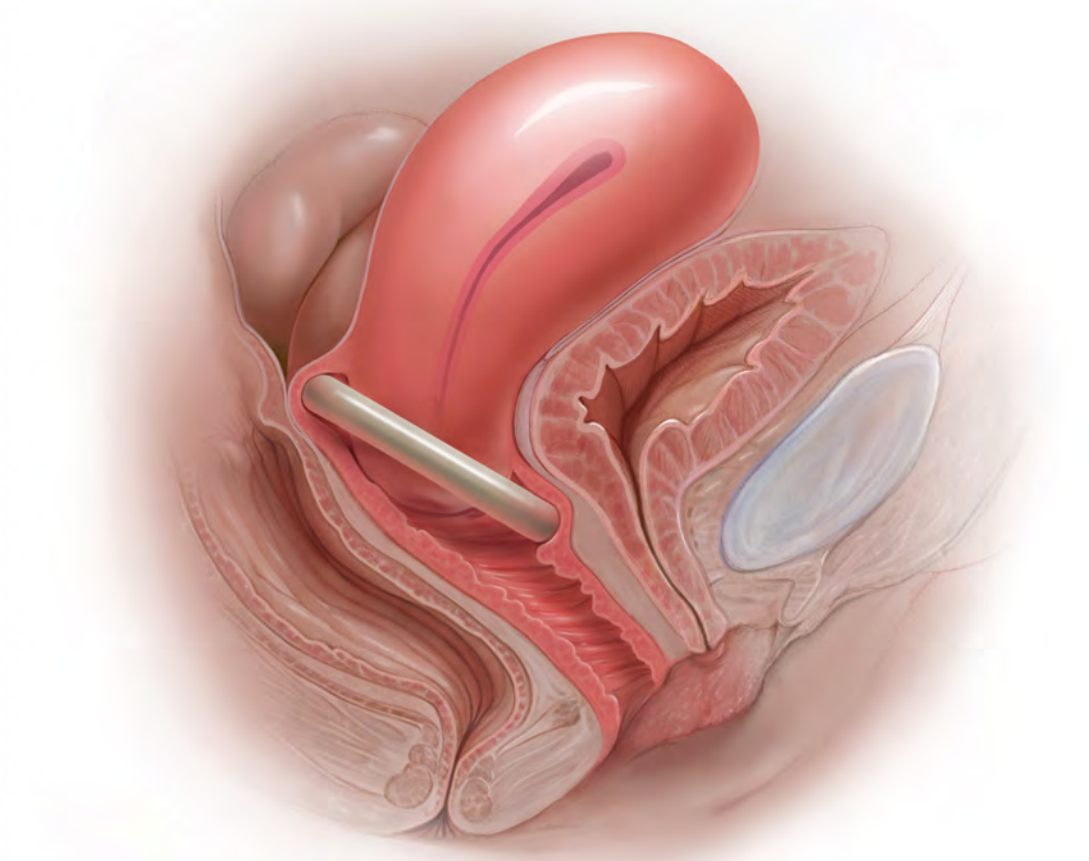


population of women at risk for POP who may be candidates for pessary use. It therefore behooves gynecologists to become familiar with the correct usage, fitting, and maintenance of this effective, nonsurgical mode of treatment for POP.

In this article, I discuss why pessaries are a good option for many patients with POP, review the types of pessaries available, and offer guidance on how to choose the right pessary for an individual patient's needs. In addition, the box on page 36 provides an interesting timeline of pessary history dating back to antiquity.

Next month in Part 2 of this article, I cover how to fit a pessary; device aftercare; potential complications of use; and effectiveness of pessaries for POP, SUI, preterm labor prevention, and defecatory disorders.

## Potential candidates for pessary use

Almost all women with POP—and in many cases accompanying SUI—are potential candidates for a pessary. In fact, many urogynecologists believe that a trial of pessary usage should be the first treatment modality offered for POP.[5] Women who cannot use a pessary include those with an extremely short vagina (<6 cm) and those who have severely eroded vaginal mucosa. In the latter situation, the mucosa can be treated with estrogen cream for several weeks and, once the tissue has healed, a pessary can be fitted.

Given that surgical repair is generally a straightforward, one-time procedure that obviates the need for long-term use of an artificial device worn internally, why might a patient or her physician opt for a pessary instead?

Some of the many reasons include:

- Many patients prefer to avoid surgery.
- Many patients are not appropriate candidates for surgery because they have significant comorbid risk factors or high BMI.
- Patients may have recurrent prolapse or incontinence and wish to avoid repeat surgery.
- Patients with SUI may have heard of the occurrence of mesh erosion and wish to avoid that possibility.
- Women who live in low-resource environments or countries where elective surgical

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

care is relatively unavailable may not have the option of surgery.

A clinician might also recommend pessary use:

- as a diagnostic tool to attempt to assess the potential results of vaginal repair surgery
- to estimate the potential effectiveness of a midurethral sling procedure; several investigators have found this to be approximately as accurate as urodynamic testing[6,7]
- as prophylaxis for pregnant women with either a history of preterm cervical dilation or a short cervix detected on ultrasonography
- for pregnant women with POP that is worsening and becoming increasingly uncomfortable
- for women with POP who wish to have more children
- for short-term use while a patient is delaying or awaiting POP surgery or to allow time for other medical issues to resolve
- for patients who wish only intermittent, temporary support while exercising or engaging in sports.

### Patient acceptance may be contingent on counseling

Numerous studies show that women who choose pessaries to treat POP are generally older than women who elect surgery. Still, patient acceptance of a trial of pessary use depends much on the counseling and information she receives. Properly informed, many patients with POP will opt for a trial of pessary placement. One study showed that, of women with untreated POP, 36% preferred pessary placement to surgery.[8] Other investigators reported that when women with symptomatic POP had the benefits of a pessary versus surgery explained to them, nearly two-thirds opted for a pessary as their mode of treatment.[9]

### Exceptions to pessary use

Fortunately, there are relatively few contraindications to pessary use. These are vaginal or pelvic infection and an exposed foreign body in the vagina, such as eroded vaginal mesh. In addition, patients at risk for nonadherence with follow-up care are poor candidates, as it could lead to missing such problems as mucosal erosion, ulceration, or even (extremely rarely) fistula formation. Pessaries may be inappropriate for sexually active women who on their own are unable to remove and reinsert pessary types that do not allow for intercourse while in place (see below).

## Types of pessaries

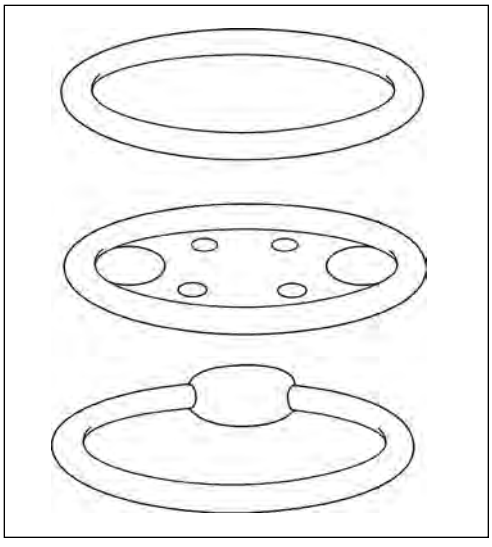
The numerous kinds of pessaries available fall into 3 general categories: support, space filling, and lever, and devices within each group have modifications and variations. As with most areas of prescribing and treatment in medicine, it is best to become very familiar with just a few kinds of pessaries, know their indications, and use them when appropriate.

Most pessaries are constructed of inert silicone which, unlike earlier rubber pessaries, does not absorb odor or discharge. They are easy to clean, long lasting, and are autoclavable and hypoallergenic.

### Support pessaries

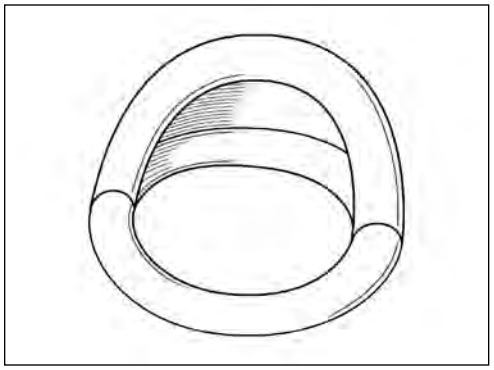
Support pessaries look like contraceptive diaphragms. They are easy to place and remove, are comfortable, and do an excellent job correcting moderate POP. They also can control or eliminate symptoms of SUI by the pressure they exert on the urethra and their alteration of the urethrovesicular angle.

Ring pessaries



DEVICE ILLUSTRATIONS: MARCIA HARTSOCK FOR OBG MANAGEMENT

Marland pessary



**Ring pessaries.** The most commonly used type of pessary, the ring pessary,[10] comes in 4 variations:

- a simple open ring
- a ring with a web of material, called a "support shield," that fills the ring
- an open ring with a firm 2-cm "incontinence knob" attached that is positioned over the urethra
- a ring with support shield and incontinence knob.

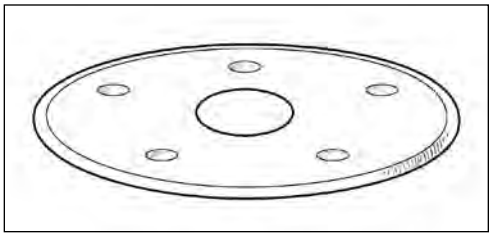
When in position, the deepest edge of a ring pessary fits behind the cervix (or in the vaginal apex for women who have had a hysterectomy) while the front of the ring slips into place behind the pubic symphysis, just like a diaphragm. When a ring with an incontinence knob is used, the ring is rotated until the knob is directly over the urethra.

Sexual intercourse is possible with any of the ring pessaries in place. Of the various types of pessaries, the ring pessary is the easiest to insert and remove. Some women tie a piece of dental floss to the edge of the ring to make its removal even easier.

The ring pessary is available in sizes 0 (44.5 mm) to 13 (127 mm). For most women a size 3, 4, or 5 ring pessary fits well.

**The Marland pessary** is similar to the ring pessary with the addition of a wedge-shaped piece of material approximately 3 cm in height that arises from half of the ring. It rarely is used in the United States because most American gynecologists are unfamiliar with it, and there is little evidence that it is more effective than the ring pessary.[11]

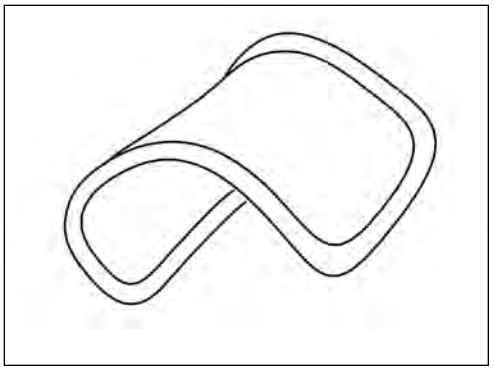
Shaatz pessary



**The Shaatz pessary** is a rigid round pessary, smaller in diameter than the standard ring pessary, and similar to the Gellhorn pessary (discussed below) but without a stem. It is placed the same way one places a ring pessary but with its concave surface up against the cervix or, if there is no cervix, against the upper anterior vaginal wall. Its main benefit is that it provides firmer support than the ring pessary. This pessary is not widely used in the United States.

**The Gehrung pessary** looks like a flat strip of material that has been bent into the shape of a "U." It is designed to correct severe cystoceles and rectoceles. For insertion, the edges at the open end of the pessary are squeezed together and the pessary is inserted with the closed part of the "U" facing the anterior vaginal wall. The upper edge is advanced until it rests in the anterior fornix of the vagina (or in the vaginal apex in women who have had a hysterectomy). Although it is more efficacious than some other pessaries for control of vaginal wall prolapse, its unfamiliarity to clinicians and its unusual shape result in it being used rarely.

Gehrung pessary



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### Space-filling pessaries

Space-filling pessaries are used when more severe degrees of prolapse are present than can be managed by the ring or other support pessaries. This is especially the case when the vagina is so capacious or the introitus so lax that a standard ring pessary cannot be kept in place, resulting in frequent expulsions.

Space-filling pessaries are 3 dimensional and work by filling the vagina with a relatively large object that prevents the cervix/vaginal apex from dropping down and the vaginal walls from prolapsing. They have a special role for women who:

- are posthysterectomy and have an enterocele and/or vaginal apex prolapse
- have significant rectoceles for which support pessaries are not effective
- have a wide vaginal hiatus and thus are prone to expel support pessaries.

Space-filling pessaries do have some drawbacks compared with support pessaries. For example, they do not help in controlling SUI, and they are difficult for patients to remove on their own for cleaning. In addition, sexual intercourse is impossible with a space-filling pessary in place.

**The Gellhorn pessary** is the most common of the space-filling pessaries, and it is the one gynecologists and urogynecologists most often use for severe prolapse. It has a concave disc that fits up against the cervix or vaginal apex and a solid stem that points down the vagina. The stem itself is supported by the perineal body. It offers excellent support for severe uterine and vaginal wall prolapse, as

## A brief history of pessaries

Pessaries have been used in one form or another to help resolve pelvic organ prolapse (POP) in women for at least 2,500 years. They have come in many shapes and have been made of many materials. Here is a brief sketch of the history of the pessary.

### Antiquity

**Kahun papyrus (ancient Egypt, c. 2000 BCE)**
Women with POP were made to stand over a fire in which different ingredients were burned. It was thought that the disagreeable odors emitted would cause the uterus to "rebel" and thus revert back into place.[1]

**Hippocrates (c. 460–375 BCE)**
Used several techniques to resolve uterine prolapse:

- Tipping the woman upside down and shaking her, using gravity as an aid to return the prolapsed organs into the pelvis[2]
- Cupping of the buttocks and the lower abdomen in hopes of "sucking" the prolapsed uterus back into place[3]

**The Greek physician Polybus (c. 400 BCE)**
Placed half a pomegranate in the vagina to hold prolapsed structures in place[2]

**Cleopatra (c. 70–30 BCE)**
Treated prolapse with the vaginal application of an astringent liquid[2]

**Celsus (c. 25 BCE–50 CE)**
Used cone-shaped pessaries made of bronze with a perforated circular plate on the lower edge through which bands were attached. The bands were then tied around the body to keep the device in place[4]

**The Greek physician Soranus (c. 98–138)**
Utilized linen tampons soaked with vinegar—along with a piece of beef—to treat prolapse. These were then held in place by bands passed around the loins[2]

**Galen (c. 130–210)**
Used fumigation to "encourage" the uterus to return to the pelvis[2]

### Middle Ages

**Paulus of Aegina (c. 625–690) and Abbas (c. 949–982)**
Both wrote about the use of pessaries made of wax[3]

**Myrepsus (late 13th century)**
Described the preparation of 45 types of pessaries consisting of different solid materials treated with perfumes, wax, honey, and herbs[5]

### 16th century

**Caspar Stromayr (*Practica Copiosa,* 1559)**
Used as pessaries tightly rolled sponges bound with string, dipped in wax, and covered with oil or butter[6]

**Ambroise Paré (c. 1510–1590)**
Developed the first ring-type pessary in the late 16th century. He used hammered brass and waxed cork in the shape of an oval to treat uterine prolapse. He also made ring-shaped devices of gold, silver, or brass which were kept in place by a belt around the waist.[7]

### 17th century

**de Castro (1546–1627)**
Urged "attacking" uterine prolapse with application of a red-hot iron thus "frightening it" into receding back into the vagina[8]

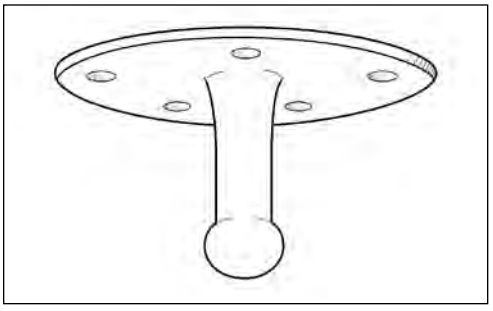
long as the perineal body is intact. The stem stabilizes the disc portion of the pessary and prevents pessary expulsion. Gellhorn pessaries are available with long or short stems.

The Gellhorn is inserted into the vagina by folding the stem 90 degrees until it is in the same plane as the disc. With lubricated fingers, the patient's perineal body is depressed and the disc of the pessary is folded and slid in. The disc is then placed up against the cervix or vaginal apex with the stem pointing down the vagina and tucked just inside the posterior edge of the introitus.

Removing the Gellhorn pessary can be problematic and is difficult for patients to do on their own. Clinicians often must use a ring forceps to grasp the stem of the pessary in order to bring it into the lower vagina, where the stem is folded up against the disc and the entire pessary removed. As with all space-filling pessaries, the Gellhorn must be taken out prior to intercourse.

The Gellhorn pessary is available in sizes that range from a disc diameter of 1.5 to

Gellhorn pessary



**Hendrik van Roonhuyse (1625–1672)**
In his gynecology textbook, discussed the etiology and treatment of prolapse. He utilized a cork with a hole in it (to allow for passage of discharge) as prolapse treatment. He also wrote of removing an obstructed wax pessary that had blocked discharge of a patient's vaginal secretions for many years[4]

## 18th century

**Thomas Simson (1696-1764)**
Invented a metal spring device that kept a pessary made of cork in place[9]

**John Leake (1729-1792)**
Recommended the use of sponges as pessaries to avoid vaginal prolapse[10]

**Juville (1783)**
Was the first to use rubber pessaries, resembling today's contraceptive cup, to avoid injuring the vaginal mucosa. The center of the cup was perforated with a gold tip which allowed for the discharge of vaginal secretions[10]

## 19th century

**Scanzoni (1821-1891)**
Recommended massage and the application of leeches to reduce local congestion and swelling of prolapsed pelvic organs before manual replacement[11]

**Hugh Lenox Hodge (1796-1873)**
In his 1860 textbook *Diseases Peculiar to Women*, Hodge discussed at length the use of pessaries for uterine displacement. He suggested that metals, alloys, glass, and porcelain be used for pessaries rather than cork, wax, and sponges[12]

## 20th century

**1950s—**
Pessaries made of rubber, which absorb discharge and odor, are replaced by polystyrene pessaries. Currently, pessaries are made of silicone, plastic, and latex.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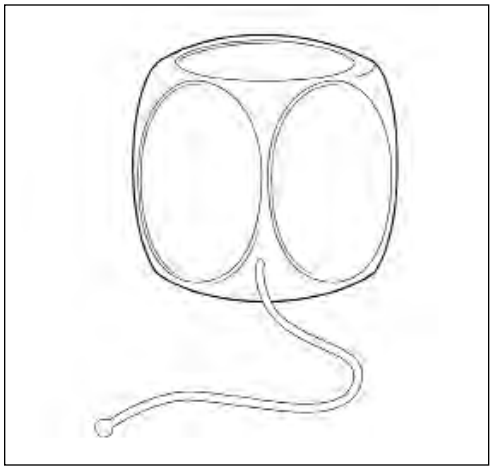
Cube pessary



3.75 inches. Those measuring 2.5, 2.75, or 3 inches are used most commonly.

**The cube pessary** is a soft, dice-shaped piece of silicone with an indentation in each of its 6 sides. It is used for severe prolapse.

Squeezing the cube allows for easier insertion into the vagina; once it is at the top of the vagina, the cube expands back to its normal shape. The indentations on each side of the cube attach to the vaginal walls with moderate suction, which helps to keep the pessary in place. Because of the suction, the cube pessary can be used in cases of severe prolapse when other pessaries will not stay in place; a drawback is that the suction created by the indented sides can cause vaginal mucosal erosion.[10] Ideally, the cube pessary should be removed every night for cleansing as discharge and accompanying odor can accumulate. The string attached to the cube pessary aids in its removal.

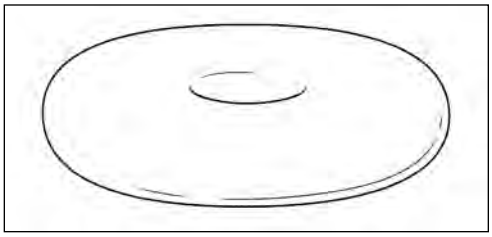
The cube pessary is available in sizes 0 to 7, with edge lengths that range from 1 to 2.25 inches.

**The donut pessary**, as its name suggests, has the form of a large donut. It can be compressed slightly to help with insertion. Because it occupies a large space within the vagina, it is used (like the cube pessary) for treatment of severe prolapse. The size and shape of the donut pessary, however, can make it difficult for patients to insert and take out on their own.

**FAST TRACK**

*Because the donut pessary occupies a large space within the vagina, it is used for treatment of severe prolapse*

Donut pessary



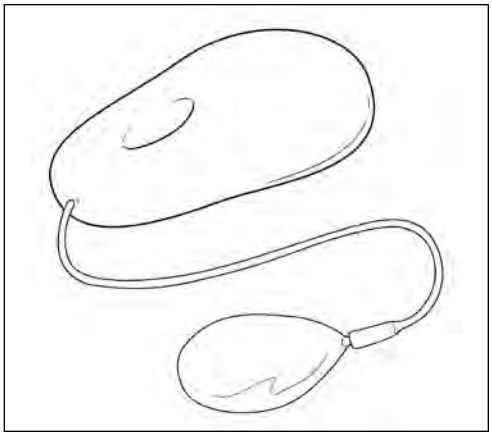
The donut pessary is available in sizes 0 (51 mm) to 8 (95 mm).

**The inflatable pessary** has the same basic shape as the donut pessary and serves the same purpose: It acts as a large semisoft object that fills the vagina to support the vaginal walls and cervix (or vaginal apex) in cases of severe prolapse. The inflatable pessary differs in that it has a valve on a stem through which air can be inserted and removed. This allows the uninflated pessary to be placed relatively easily into the vagina and then pumped full of air to the dimensions necessary to prevent vaginal, cervical, uterine, or apex prolapse. Air likewise can be removed to facilitate pessary removal.

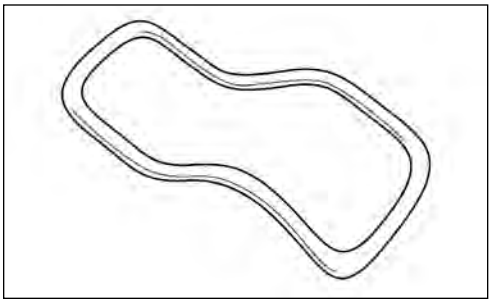
One drawback of the inflatable pessary is that it is made of latex and thus cannot be used by anyone with a latex allergy. Also, as latex retains discharge and odors, this pessary should be removed and washed daily.

The inflatable pessary is available in sizes that range from 2 to 2.75 inches in 0.25-inch increments.

Inflatable pessary



Lever pessary



### Lever pessaries

In addition to the more commonly used support and space-filling pessaries, there is a third kind that is rarely used in current practice: the lever pessaries. These pessaries—the **Hodge,** the **Smith,** and the **Risser**—are rectangles made of inert plastic that are folded into 3 planes to facilitate positioning in the vagina. The narrower of the 2 shorter ends of the folded rectangle is placed behind the cervix or at the vaginal apex while the other short end is placed behind the symphysis pubis.

Although sometimes used to correct POP in nonpregnant women, the lever pessary's main purpose is to antivert a retroflexed uterus and to support the cervix and uterus in cases of prolapse during pregnancy or impending cervical incompetence.

The 3 lever pessaries differ in terms of whether the narrow ends of the pessary are straight or curved and wider or narrower.

## How to choose the right pessary for your patient

If a patient's POP or urinary incontinence symptoms would best be treated with a pessary, the next step is to select the pessary type and size best suited for that patient's needs and the size that should be prescribed. While there is controversy among experts as to whether or not certain pessaries are better than others for different indications,[12] most gynecologists and urogynecologists who use pessaries on a regular basis agree on the following:

**1. Support pessaries will meet the needs of most women with moderate POP and/or SUI.** These include the ring pessary with or without the support shield and with or without an incontinence knob. A support pessary is the go-to pessary in most cases. Most women find it comfortable to wear, it is easy to put in and take out, and sexual intercourse is possible with the pessary in place.

**2. The specific degree of a patient's prolapse and/or incontinence** dictates whether or not to prescribe the support shield feature or the incontinence knob with a ring pessary. The shield helps support a prolapsed cervix and uterus when they are present.[5,13] The knob is a useful feature if incontinence is a prominent symptom.

**3. The Gellhorn pessary is usually the first choice for more severe prolapse.** As long as there is some degree of posterior perineal support, this pessary does an excellent job of correcting even severe prolapse whether of a cervix and uterus or of vaginal walls and apex. It does require the patient to have some practice and dexterity for inserting and removing it on her own; individuals not comfortable or physically able to do so will need to have the pessary removed and cleaned by a clinician on a regular basis in the office. (Part 2 of this article will discuss pessary cleansing intervals).

**4. Space-filling pessaries (such as the cube and donut) are useful when there is a severe degree of prolapse and insufficient perineal support to maintain a Gellhorn pessary.** In practice, they are generally used less frequently—which is unfortunate, as they are a potentially useful solution for older women with severe prolapse who might not be candidates for surgical repair. As mentioned, both the cube and donut pessaries require more frequent removal for cleaning.

**5. In unusual cases, the use of 2 pessaries simultaneously may resolve a difficult problem,** such as when a pessary is the only option for treatment, the prolapse is severe, or it is impossible to find a pessary that resists being expelled from the vagina.[14] A space-filling pessary in the most cephalad aspect of the vagina used in conjunction with a ring pessary with support shield below it can sometimes resolve even the worst cases of prolapse.

CONTINUED ON PAGE 44

BREAK THIS PRACTICE HABIT

# Replace routine preoperative testing with individualized risk assessment and indicated testing

Evidence indicates no benefit for certain testing that has, to this point, been considered standard practice for low-risk patients undergoing noncardiac surgery, say these authors

**Emily B. Wang, MD, MPH, and Kimberly A. Kho, MD, MPH**

IN THIS ARTICLE



**CASE Patient questions need for preoperative tests**

A healthy 42-year-old woman (G2P2) with abnormal uterine bleeding and a 2-cm endometrial polyp is scheduled for hysteroscopic polypectomy. After your preoperative clinic visit, the patient receives her paperwork containing information about preoperative lab work and diagnostic studies. You are asked to come into the room because she has further questions. When you arrive, the patient holds the papers out and asks, "Is all this blood work and a chest x-ray necessary? I thought I was healthy and this was a fairly simple surgery. Is there more I should be worried about?"

How would you respond?

The goal of preoperative testing is to determine which patients may be at an increased risk for experiencing an adverse perioperative event, taking into account both the inherent risks of the surgical procedure and the health of the individual patient. In the literature, the general consensus is that physicians rely too heavily on unnecessary laboratory and diagnostic testing during their preoperative assessment.[1] More than 50% of patients who underwent preoperative evaluation had at least 1 unindicated test.[2] These tests may result in a high frequency of abnormal findings, with less than 3% of abnormalities having clinical value or leading to a change in management.[3]

With health care costs accounting for almost 20% of the gross domestic product in the United States (totaling about $3.5 billion in 2017), performing unindicated preoperative testing contributes to the economic burden on health care systems, with an estimated cost of $3 to $18 million annually.[4,5] In addition, unindicated tests can increase patient anxiety and necessitate follow-up testing, possibly exposing physicians to increased liability if abnormal results are not adequately investigated.[6]

It is time to rethink our use of routine preoperative testing.

## Which tests to consider—or not: Evidence-based guidance

Professional societies, including the American Board of Internal Medicine's Choosing

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*Dr. Kho reports serving on the scientific advisory board for Myovant Sciences. Dr. Wang reports no financial relationships relevant to this article.*

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**TABLE 1** Physical status classification system of the American Society of Anesthesiologists[8]

| Class | Definition | Examples including, but not limited to |
|---|---|---|
| ASA I | Normal healthy patient | Healthy, nonsmoker, no or minimal alcohol use |
| ASA II | Mild systemic disease | Mild disease only without substantive functional limitations: current smoker, social alcohol drinker, pregnancy, obesity (BMI, 30-40 kg/m$^2$), well-controlled DM/HTN, mild lung disease |
| ASA III | Severe systemic disease | One or more moderate-to-severe diseases with substantive functional limitations: alcohol dependence or abuse, poorly controlled DM/HTN, COPD, morbid obesity (BMI >40 kg/m$^2$), active hepatitis, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regular scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents |
| ASA IV | Severe systemic disease that is a constant threat to life | Recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunctional severe reduction of ejection fraction, sepsis, DIC, ESRD not undergoing regularly scheduled dialysis |

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; MI, myocardial infarction; TIA, transient ischemic attack.

Wisely campaign, promote a move away from routine testing to avoid unnecessary visits and studies. In addition, the American Society of Anesthesiologists (ASA) has published recommendations to guide preoperative testing.[7] To stratify patients' surgical risk according to their pre-existing health conditions, the ASA created a physical status classification system (**TABLE 1**).[8]

In addition to individual patient characteristics, some guidelines similarly stratify surgical procedures into minor, intermediate, and major risk. The modified Johns Hopkins surgical criteria allocates surgical risk based on expected blood loss, insensible loss, and the inherent risk of a procedure separate from anesthesia (**TABLE 2**, page 42).[9] Despite these guidelines, physicians responsible for preoperative evaluations continue to order laboratory and diagnostic tests that are not indicated, often over concerns of case delays or cancellations.[10,11]

The following evidence-based recommendations provide guidance to gynecologists performing surgery for benign indications to determine which preoperative studies should be performed.

## Serum chemistries

**Basic metabolic panel (BMP).** In both contemporary studies and earlier prospective studies, a preoperative BMP has a low likelihood of changing the surgical procedure or the patient's management, especially in patients who are classified as ASA I and are undergoing minor- and intermediate-risk procedures.[12,13] Therefore, we recommend a BMP for patients in class ASA II or higher who are undergoing intermediate-risk or major surgery.[14]

**Thyroid function.** A basic tenet of preoperative evaluation is that asymptomatic patients should not be diagnosed according to lab values prior to surgical intervention. Therefore, we do not recommend routine preoperative thyroid function testing in patients without a history of thyroid disease.[10] For patients with known thyroid disease, a thyroid stimulating hormone (TSH) level should be evaluated prior to major surgery, or with any changes in medication dose or symptoms, within the past year.[15]

**Liver function tests (LFTs).** Routine screening of asymptomatic individuals without risk factors for liver disease is not recommended because there is a significantly lower incidence of abnormal lab values for LFTs than for other lab tests.[16] We recommend LFTs only in symptomatic patients or patients diagnosed with severe liver disease undergoing intermediate-risk or major procedures.[14]

**Hemoglobin A1c (HbA1c).** Poorly controlled diabetes is a risk factor for poor wound healing, hospital readmission, prolonged hospitalization, and adverse events following surgery.[17] We recommend that HbA1c

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*In addition to individual patient characteristics, some guidelines similarly stratify surgical procedures into minor, intermediate, and major risk*

**TABLE 2 Estimating surgical risk**[9]

| Surgical risk | JHRCS category | Description | Expected blood loss | Exclusions | Examples[a] |
|---|---|---|---|---|---|
| Minimal | 1 | Minimal risk to patient independent of ASA<br>Often done in office setting, operating room primarily used for anesthesia/monitoring | Little or none | Open exposure of internal organs<br>Entry into abdomen<br>Placement of prosthetic devices<br>Planned postoperative ICU care | Hysteroscopy<br>Wide local excision<br>Loop electrosurgical excisional procedure<br>Dilation and curettage |
| Intermediate | 2 | Minimal to moderate invasive<br>Mild risk to patient independent of anesthesia | <500 mL | Open exposure of internal organs<br>Placement of prosthetic devices | Diagnostic laparoscopy<br>Myomectomy<br>Laparoscopic lysis of adhesions, ovarian cystectomy, resection of endometriosis<br>Laparoscopic/vaginal hysterectomy |
| Major | 3 | Moderately to significantly invasive<br>Moderate risk to patient independent of anesthesia | 500-1,000 mL | Major vasculature repair<br>Open thoracic or intracranial procedures<br>Planned postoperative ICU care | Abdominal hysterectomy<br>Myomectomy (multiple)<br>Resection of Stage IV endometriosis<br>Emergent procedures[b] |
| Major + | 4 | Highly invasive<br>Major risk to patient independent of anesthesia | >1,500 mL | | Major gastrointestinal tract reconstruction |

Abbreviations: ASA, American Society of Anesthesiologists; ICU, intensive care unit; JHRCS, John Hopkins risk classification system.
[a]Modified JHRCS to add examples of gynecologic procedures.
[b]Emergent procedures considered major due to insufficient time to evaluate comorbid conditions.

levels be drawn only for patients with known diabetes undergoing intermediate-risk or major surgery who do not have an available lab value within the past 3 months.[14]

## Hematologic studies

**Complete blood count (CBC).** Many patients undergoing gynecologic procedures may have unreported or undiagnosed anemia secondary to abnormal uterine bleeding, which also may encompass heavy menstrual bleeding. With an abnormal CBC likely to affect preoperative management, assessment of preoperative hemoglobin levels is critical so that hemoglobin levels can be appropriately corrected before surgery. We therefore recommend obtaining a CBC for patients in class ASA II or higher who are undergoing intermediate-risk or major surgery.[10,14]

**Coagulation studies.** Preoperative coagulation studies are unlikely to uncover previously undiagnosed inherited coagulopathies, which are generally uncommon in the general population, and they do not predict operative bleeding when ordered unnecessarily.[18,19] Therefore, we recommend preoperative coagulation studies only in patients 1) currently on anticoagulation therapy undergoing intermediate-risk or major surgery or 2) in class ASA III or higher with bleeding disorders or cirrhosis undergoing intermediate-risk or major surgery.[14]

**Type and screen (T&S).** Complicated algorithms have been proposed to determine when a preoperative T&S is necessary, but these may be impractical for busy gynecologists.[20] We recommend a T&S within 72 hours, or on the day, of surgery for all patients undergoing major surgery, including hysterectomy, or with an anticipated blood loss of more than 500 mL; routine cross-matching of blood is not recommended.[10,14]

### Urologic studies

**Urine pregnancy test.** Although the probability of a positive pregnancy test is likely very low, its occurrence frequently leads to the cancellation of surgery. We therefore recommend a preoperative urine pregnancy test, particularly in reproductive-aged patients with unknown pregnancy status or unreliable contraceptive habits.[14] Preoperative urine pregnancy testing, even in patients who report sexual inactivity, ideally should be individualized and based on risk of fetal harm during or subsequent to surgery. Surgeries involving the uterus, or those involving possible teratogens like radiation, also should be considered when making recommendations for testing.

**Urinalysis and urine culture.** In asymptomatic patients undergoing general gynecologic procedures, a routine preoperative urinalysis and urine culture are of little value.[18] However, among patients undergoing a urogynecologic surgical procedure, the risk of a postoperative urinary tract infection is higher than among patients undergoing a nonurogynecologic procedure.[21,22] Therefore, we typically do not recommend routine preoperative urinalysis or urine culture, but a preoperative urine culture may be beneficial in patients undergoing urogynecologic surgery.[14]

### Diagnostic studies

**Electrocardiography (ECG).** The absolute difference in cardiovascular death is less than 1% among patients with and without ECG abnormalities undergoing a noncardiac procedure with minimal to moderate risk; therefore, routine ECG for low-risk patients should not be performed.[23] Instead, ECG should be performed in patients with known coronary artery disease or structural heart disease and in patients aged 65 years and older, since age older than 65 years is an independent predictor of significant ECG abnormalities.[24,25] We therefore recommend that the following individuals have an ECG within the last 12 months: patients aged 65 years and older, patients in class ASA II or higher with cardiovascular disease, and patients in class ASA III or higher undergoing general anesthesia. If there is a change in cardiovascular health since the most recent ECG—even if it was performed within 12 months—a repeat ECG is warranted.[10,14]

**Chest x-ray.** Despite a high rate of abnormalities seen on routine and indicated chest x-rays, there is no significant difference in perioperative pulmonary complications among patients with a normal or abnormal chest x-ray.[16] Rather than changing surgical management, these abnormal results are more likely to lead to the cancellation or postponement of a surgical procedure.[7] We therefore recommend against routine preoperative chest x-ray.[14]

## The bottom line

Preoperative testing serves as an additional component of surgical planning. The fact is, however, that abnormal test results are common and frequently do not correlate with surgical outcomes.[26] Instead, they can lead to unnecessary surgical procedure cancellations or postponements, undue anxiety in patients, increased liability among physicians, and rising health care costs.[5-7]

Rather than overly relying on routine laboratory or diagnostic studies, the history and physical examination should continue to be the cornerstone for surgeons responsible for assessing surgical risk. With individualized risk assessment, specific, indicated testing rather than routine nonspecific testing can be obtained.[10,14] In short, low-risk patients undergoing noncardiac surgery are unlikely to benefit from preoperative ECG, chest x-ray, or routine laboratory testing without clinical indication. ●

*For Table 3: Recommendations for preoperative testing, read the online version of this article at mdedge.com/obgyn.*

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*We recommend a preoperative urine pregnancy test, particularly in reproductive-aged patients with unknown pregnancy status or unreliable contraceptive habits*

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## Replace routine preoperative testing with individualized risk assessment and indicated testing

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## Pessaries

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### Stay tuned

Part 2 of this article next month will provide more information on pessaries, including fitting, aftercare, potential complications, and effectiveness in various disorders. ●


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# Facing systemic racism in health care: Inequities in medical education

These experts discuss the realities of systemic racism that one Black male medical student faced on his journey to fulfilling his dream of becoming an ObGyn

**Barbara Levy, MD, and Pierre Johnson, MD**

OBG MANAGEMENT takes the issues of systemic and structural racism incredibly seriously--not just by talking about it but by trying to highlight areas in medicine, particularly in obstetrics and gynecology, that are barriers to progress. In this new series for OBG MANAGEMENT, Board Member Barbara Levy, MD, faces the issues head-on, beginning with this peer-to-peer interview with Pierre Johnson, MD, ObGyn in Chicago, Illinois. Watch for future installments in upcoming issues of OBG MANAGEMENT.

## Finding inspiration among life's challenges

**Barbara Levy, MD:** I am fortunate to have met Pierre serendipitously at a training that we were both attending and was impressed by Dr. Johnson's life story, his passion and commitment, and his dedication—not only to his personal career but also to raising up other young men of color by trying to break down barriers that face them. His life story highlights those areas of systemic and structural problems that all of us together need to address if we are going to make any progress.

**Pierre Johnson, MD:** Thank you, Barbara. A little about myself: I am a board-certified ObGyn, and I specialize in minimally invasive surgery. I was born on the South side of Chicago, experiencing gang violence, drugs, and substandard, underserved schools. Long story short, I had a very rough upbringing. I had a single mom and several different issues at home. I am the oldest of 5 siblings, and life was tough.

But I knew that I wanted to do something different with my life. I saw that there was a need in my community as far as health care was concerned, in particular women's health and childbirth. I knew early on that I wanted to be an ObGyn, and the reason had a lot to do with *The Cosby Show*. It was the only example of a positive, successful Black man that I saw. No one graduated from college in my family. There weren't any models of young Black excellence around me. Saying that I wanted to be a doctor planted a seed. I was 9 when my mom became pregnant with my first sibling, and it was fascinating to me. The physiology of pregnancy, and eventually childbirth, was extremely fascinating to me; it set me off on my journey to be an ObGyn.

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As I got older, things didn't get any easier. I went to high school in one of the toughest areas on the South side of Chicago. Gang violence, and violence in and of itself, were all around me, but I was able to stay focused. I went on to Xavier University in Louisiana.

**Dr. Levy:** There are some important things that I learned from your book and from talking to you at our first meeting. Your mom's ObGyn, when she was pregnant with your next youngest sibling, was also a Black ObGyn. He took some time to take you under wing?

**Dr. Johnson:** He did. My mom's ObGyn was a Black man. Other than *The Cosby Show*, that's the only time I saw something like that. When I spoke to him, he really took the time to answer my questions and show me that he was like me; he wasn't just a far-off mythical person, or something that I could not obtain.

### Seeing is believing when it comes to success

**Dr. Levy:** Do you think it was important to have a role model who wasn't a sports star?

**Dr. Johnson:** If you can't see it, you can't achieve it. He took his time to really talk to me, and it's the little things for kids that go a long way in their life experience. I still have a relationship with him to this day. How he handled me as a kid made me realize that this is something that I could do. That was extremely important for me.

**Dr. Levy:** One of the structural things I think we need to point out is that the ability to see yourself as someone successful is critical. When we see 1,000 images a day and they are all White, and they are all so different from where we are that it gets incorporated into our sense of being. I think that's really difficult for those of us of with privilege to understand what that privilege is.

**Dr. Johnson:** Absolutely, and I'll even go further. In residency, 2 White females were my classmates, and both of their parents were doctors. They had grandparents who were doctors. My mom was addicted to drugs; my father was not around. They had been talking medicine since they were 5. You have to make things equitable, but in medicine it's really not equitable. In medicine, what we don't realize is that there is an importance for all aspects of someone's upbringing and environment, and it's not just what they can regurgitate on a standardized test. If a patient can't relate to you and tell you what is wrong with them, how can you adequately treat them?

**Dr. Levy:** Even if they are trying to tell me, but I can't hear it because I don't have the language and I don't have the background. There are really good data to show, in fact, that Black male physicians do a better job at engaging Black men to manage their hypertension.[1] When we look at the inequities in birth outcomes for women of color, indigenous women and Black women, there's evidence that providers who come from a similar background do a better job.

**Dr. Johnson:** There was the study of Black infants that just came out about them dying at a 3-time higher rate in non-Black physicians' hands.[2] These things need to be recognized. They need to be discussed, and they need to be identified as issues and then, realistically, we need to start talking about solutions, not get offended by what actual statistics are saying.

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*"In medicine, what we don't realize is that there is an importance for all aspects of someone's upbringing and environment, and it's not just what they can regurgitate on a standardized test."*

## Foundational inequities in education

**Dr. Levy:** To address some of the barriers that you faced: I know that you went to a high school that was not geared toward pushing students into professional careers. Your colleagues, however, had educations that prepared them for the standardized tests and other things that they would face academically.

**Dr. Johnson:** People think I am kidding when I say it, but when I went into college, I didn't know what a periodic table was. I saw it, but I had no idea what these things meant. I didn't have any sciences or any AP classes in high school. I did well, but grades are smoke and mirrors. The true test of medicine comes with testing. From the MCATs to the boards, every step of the way there is a standardized test.

Knowledge is something that you can obtain, but test taking is a cultivated skill that happens from a very early age. Trying to teach an adult or someone in their late teens a skill that they should have learned as a kid is

difficult. For me, I did not have that, so I had to program myself. I had to learn how to fundamentally take tests as an adult, where most people understand how to do that going into college and professional school.

**Dr. Levy:** I was impressed with your resilience. I think all of us as human beings, if we fail a test, we take it personally and think it's about our lack of knowledge. One of the insights that you came to was that failure on those things was not that you didn't study hard enough. In fact, you probably studied 4 times harder than most other people. You had the knowledge. Being able to get that knowledge into a standardized structured test score was the huge challenge for you.

**Dr. Johnson:** That's it. I can remember taking the MCAT, and if you looked at the step 1 book, I could regurgitate to you everything on that page. However, it's not a test about do you know it or not. It's an understanding of the English language and how to break things down to make things fit into particular scenarios.

## A college experience focused on growth and exposure

**Dr. Levy:** I was impressed by the distinction between your experience at Xavier University where there was a lot of support and guidance and help in your premed program, and what happened to you when you hit medical school.

**Dr. Johnson:** Xavier University in Louisiana is the number 1 institution in the country for getting minorities into professional school. They understand that they have kids that are brilliant but underprepared, and just have not had the background to actually tackle some of these tough curriculums. I always had good grades in school. But by not being challenged, I didn't know what I didn't really know. So now that I was seeing biology, chemistry for the first time, and trying to tackle it; there's a failure point. I didn't know how to take tests, and I didn't know how to study properly. The harder I tried, the worse things got for me.

Xavier has seen that story a multitude of times. If I went to a bigger or predominantly White university, a counselor would have told me, "Well, medicine's maybe not for you. You can't handle a premed curriculum." Instead, I said, "Listen, I'm studying. I'm doing all of these things, and I'm not hacking it." And they broke it down: "Let's get you into study groups with kids that have had these type of AP classes before. We'll have you watch how they study," and everything started to click. That facilitation of how to adjust to this curriculum was a godsend. It's the only reason I'm here. I am a prime example of being brilliant enough to be able to do it, but needing the infrastructure and a system set up.

**Dr. Levy:** There's a great book by Carol Dweck called *Mindset* that talks about education of young kids and putting them into silos so early in life; the brilliant kids go into the AP courses and the rest are labeled as inadequate. It's assumed in a fixed mindset based on their heredity and IQ, and not based on the fact that they have not been exposed to the right things.

Xavier was growing you into the man who could, in fact, do all of those things. I think that is one of the systemic and structural issues that we have—that fixed mindset that frames a kid who is not succeeding as therefore unable to succeed, as opposed to framing that child as not having the correct tools.

## New tribulations of medical school

**Dr. Johnson:** Absolutely. I think what Xavier did for me is to at least let me understand what I needed to do, how to comprehend and retain information, which I never had been exposed to before. Those years were very important to establishing a foundation. When going to medical school, it was like, "There's no more excuses. What could be the problem now?" Well, now let's talk about taking tests—a whole different skill. Xavier focused on getting me to understand how to structure my thought process and knowledge base. In medical school I had to apply those skills (because if you can't apply them, there's no fit).

My second through fourth year of medical school, I was the only African-American kid in my class. I was spending 20-hour days sometimes just studying, trying to overcompensate by knowing as much as I possibly could and thinking that would propel me from the test-taking standpoint. Even though

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*"I think that is one of the systemic and structural issues that we have—that fixed mindset that frames a kid who is not succeeding as therefore unable to succeed..."*

I didn't have a lot of classmates in medical school that looked like me, I did have mentors that looked similarly, who really saw potential in me. Dr. Frederick Horvath, a nephrologist in Peoria said, "What are you doing? I want you to get out of these books, and let's go out to lunch."

He ended up buying me some instrumental books, really talked to me, listening to my background and understanding how driven I was as a person. He took me under his wing for the rest of medical school and said, "This is how you navigate through these spaces. Yes, you need to have a fund of knowledge to be able to take these tests, but you need to start understanding how to apply it to these questions." I'm forever grateful to Dr. Horvath for doing that because it was a point in time where I was lost and struggling.

## Hitting a stride but facing racism head-on

**Dr. Levy:** You talk about the systemic and pervasive racism that was on the wards when you hit them in fourth year. If you don't mind sharing just a little bit of that, it would help people reading this to have a better understanding of the kinds of barriers that are out there.

**Dr. Johnson:** Even when I talk about it today, it bothers me.

I went to medical school in Peoria, Illinois, not far from the home of the Ku Klux Klan. At that time, once you got out of Chicago it was a very brutal place, with systemic racism throughout. I was a young Black kid going through a process that not many young Black kids from the South side of Chicago go through, and you had people who had never seen anyone like me. When I was going through my clinical rotations, I knew what I was up against. I was dressed "to the T" every day, arriving early, leaving late, trying to answer questions. I would look at the evaluations, and they would be disparaging. I would look at my counterparts, how their evaluations were, and how people would respond to them, and it would be completely different.

Surgery was the part of ObGyn that I really grew to love more than anything, even more than obstetrics. When general surgery came, I wanted to take it very seriously and learn as much as I possibly could. From the beginning, I knew there was a problem because the chief resident, an older White man, wouldn't look me in the eye or talk to me. He would make disparaging remarks. The thing that stuck out in my mind the most was when I was in the operating room transporting patients, just like a medical student did, and he came up behind me and said, "You know, Pierre, this is where a small mind and a strong back come into play." For me, it took me to a place where I had to corral my emotions and thoughts because I just wanted to lash out and just tell him how racist and horrible that was for him to say that to me. I explained this to the powers that be, the director of the department, and they basically blew it off to the side.

When it came down to the end of the evaluation period, I passed with flying colors. But they gave me an incomplete because of that chief resident and his remarks on my evaluations. He had 3 pages of report about me as a person and as a student. He said that he had difficulty in expressing his opinions about me because of possible cultural biases that he may have had. He put "cultural biases" in an evaluation, and they looked at that and said that was enough for me to have to remediate my time. I was required to do an extra month in Pontiac, Illinois, which is even more rural than Peoria, because of a racist person that did not give me a fair opportunity because I was Black.

Like everything else in life, it was a learning experience. It's why I fight so hard today. It's why I'm so passionate about equity, not only in medicine but also in all aspects of society. It shows why we have police brutality and Black men dying in the streets. It shows how this happens because there are cultural and implicit biases that play out in every part of life, and we are not honest about it. Until we are honest about it and until we say that this is happening and there is something that needs to be done to address it, it's going to continue to happen. That is my fight.

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*"...there are cultural and implicit biases that play out in every part of life, and we are not honest about it."*

### Exposing the unspoken power struggle

**Dr. Levy:** I couldn't agree more. Attributing things like that to the individual, where you talk about a White man in power and a power structure that didn't literally physically beat you but did beat you into submission. You talk about how to succeed in medical school, and how you had to suck it up and submit to something that was incredibly unfair. You understood, you were old enough, mature enough, to understand that if you fought back, you were going to lose. The only opportunity you had was to submit to that inequity and push forward.

**Dr. Johnson:** When I did try to fight, the chair of the department told me that either I accept the consequences or I would not graduate from medical school and be forced to do another year. That struck a chord with me. I think that happens a lot in our society, and it needs to be exposed.

## Past experiences reflected in today's society

**Dr. Levy:** Can you talk about what you faced in your ObGyn residency in terms of the systemic pushback, people not taking your orders, people questioning you. I know that I have heard that a great deal, and I experienced that myself as a woman.

**Dr. Johnson:** We look at the things that are happening now, everything from George Floyd's murder to Colin Kaepernick taking a knee. These things are 10 years past when I first started residency. The year before I started residency, there was a noose hanging on the capitol lawn of Springfield, Illinois' capital city. There's systemic racism and hatred there. When I first started on the wards of my first year of ObGyn, again, I was the very first Black resident of my program's history. Nobody could relate to me.

I went from a year-long general surgery internship at Washington Hospital Center in Washington, DC, to ObGyn residency. In the first 2 months, there were complaints of, "He's not answering his pages. He's not being prompt." I went to my program director and said, "Listen, I have never had one complaint like this. There's a problem here. And there's a problem when I'm on the floor: When trying to give orders to nurses, they're not taking them. I had to tell a couple of nurses, 'I'm Dr. Johnson. Don't call me by my first name, especially not in front of patients.'"

My director was just not hearing me, because the entire scenario was something they had never been exposed to. Systemic racism is real, and unless you experience it, it's very difficult to accept that it is happening. But biases happen when you are not cognizant. People are used to things a certain way. Things play out in the media that make your mind think a certain way, and you don't even realize it. You may not even want to be that way.

### Unconscious bias is a barrier to ensuring equity

**Dr. Levy:** One very important point you just made is that we as the system need to be able to recognize those unconscious things, the language that we use, the disparaging remarks, the things that put people down, as well as the things that keep people out of promotion.

There are some interesting data about both race and gender and the language that we use when we write recommendations for people, that we do things unconsciously. The big message to all of us at the end is to open our minds to where those things can occur. For myself, professionally, I keep a list of words that I use when I write recommendations. I measure myself to ensure that I am using the same language for men and women, for Black and White. I think we need to overcome the system and the structure to create real equity—not equality but equity.

### It begins with being real about the issues

**Dr. Johnson:** It's a bigger problem than the existence of bias and racism. I think these are systemic issues that have been cultivated over centuries that have never been addressed. The true issue is that we deny that these are problems and refuse to talk about it because it makes us uncomfortable. To truly make things more equitable, we have to push our levels

**FAST TRACK**

*"To truly make things more equitable, we have to push our levels of comfort to be able to talk about things in a healthy manner, be open and transparent, and to start to understand how we are thinking about certain things."*

## Resources

- *The Pulse of Perseverance: Three Black Doctors on Their Journey to Success*
  Pierre Johnson, MD; Maxime Madhere, MD; and Joseph Semien Jr, MD
- *Mindset: The New Psychology of Success*
  Carol S. Dweck

of comfort to be able to talk about things in a healthy manner, be open and transparent, and to start to understand how we are thinking about certain things. When you can see it, you can start to implement changes and start to change mentalities and thought processes.

For me, people say, "You don't look like a doctor." I get that all the time—because I have tattoos and earrings. I wear my hair in a mohawk. The image of what success looks like has been manifested through our media and culture, and it has imprinted on our minds as to how things are supposed to be. If someone doesn't fit those molds, we start to shun them out, or we start to exhibit biases against those things. What I am trying to do is change that thought process of what a successful or a professional person looks like. It doesn't have a look. It is not a White or Black thing. It's an intellect, a mindset, a way of living. You have to treat every person as an individual and take all the biases out of it and understand where they are coming from and what they have to offer to the profession.

**Dr. Levy:** I personally was so impressed by you when I met you. I was impressed by the tattoos and the earrings, and my initial response to them was exactly that biased, "Oh, who is this person?" I checked that at the door, listened to you, and was really impressed at your surgical skill, your knowledge, your background. I am really grateful that you have been willing to spend the time to share that with everyone.

**Dr. Johnson:** Thank you for this discussion.

*To watch the full interview between Drs. Levy and Johnson, visit: https://www.mdedge.com/obgyn/article/228507/facing-systemic-racism-health-care-inequities-medical-education.* ●

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## COMMENTARY

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