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OBG MANAGEMENT

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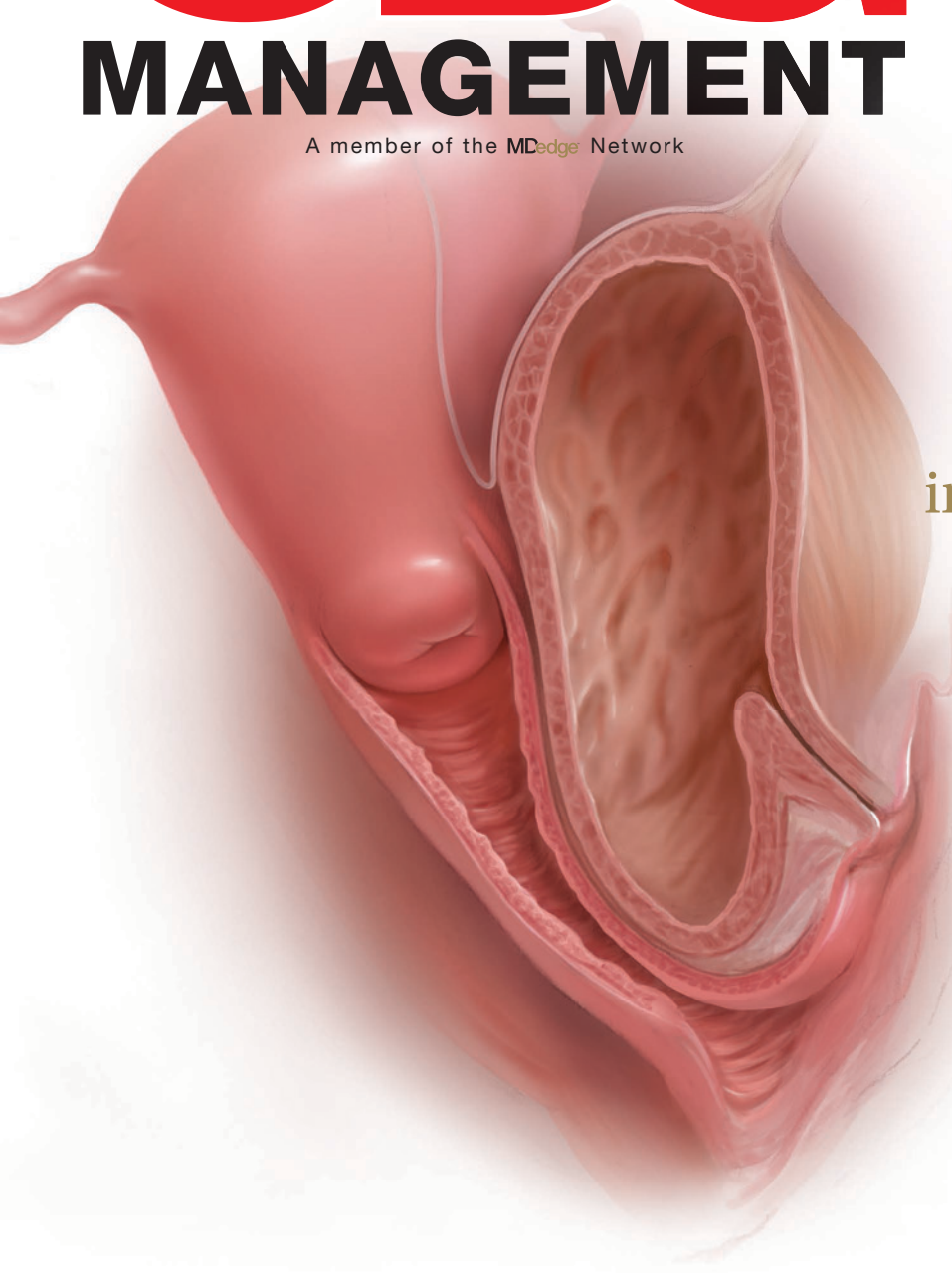
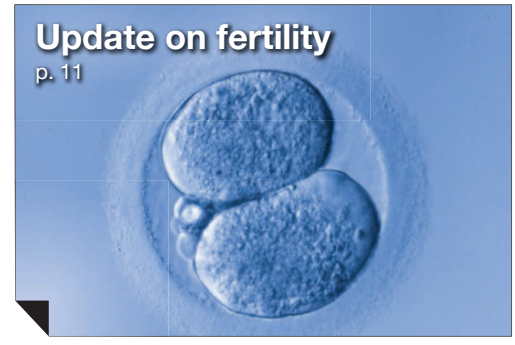


Pelvic organ prolapse

A roundtable including expert tips for management

Featuring
John B. Gebhart, MD, MS;
Mickey M. Karram, MD;
Beri M. Ridgeway, MD;
and Mark D. Walters, MD



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

TAKE ON SUBOPTIMAL SCREENING RATES

ONE YES AT A TIME

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

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

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

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

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

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

Indication and Important Risk Information

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

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

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

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

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

Offer a highly effective, noninvasive CRC screening option to your appropriate average-risk patients aged 45 years or older.

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

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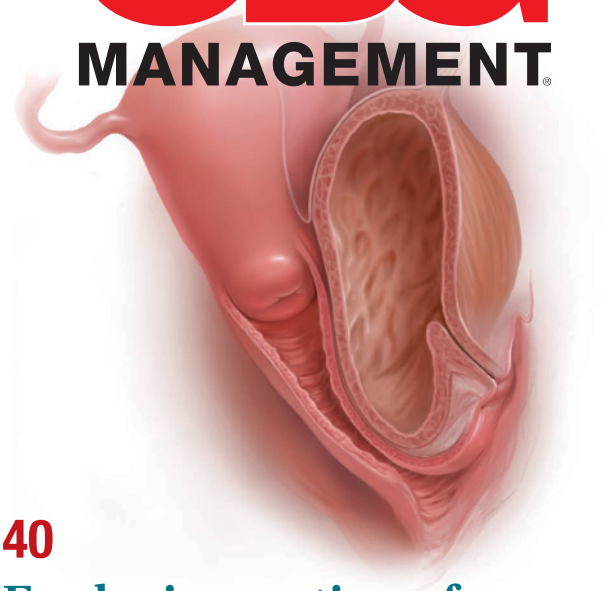

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HT for hot flashes

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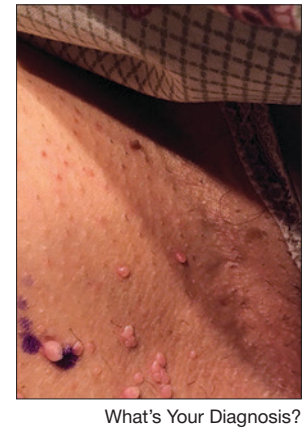

What's Your Diagnosis?

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

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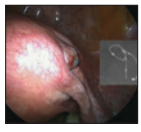

Laparoscopic techniques for Essure device removal

LINDA C. YANG, MD; LINDSAY MCALARNEN, MD, MSC; AND MARY MCKENNA, MD

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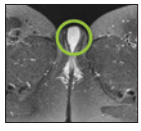

A clitoral cyst of "epidermal" proportions

ANGELA DICARLO-MEACHAM, LCDR, MC, USN; KATHERINE L. DENGLER, MAJ, MC, USA; ANDREA N. SNITCHLER, CDR, MC, USA; AND DANIEL D. GRUBER, COL, MC, USAF

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EDITORIAL

Progestin-only systemic hormone therapy for menopausal hot flashes

Clinicians treating postmenopausal hot flashes often recommend "systemic estrogen treatment." However, progestin-only therapy also can effectively treat hot flashes and is an option for women with a contraindication to estrogen therapy.

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Chair, Obstetrics and Gynecology
Brigham and Women's Hospital
Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
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The field of menopause medicine is dominated by studies documenting the effectiveness of systemic estrogen or estrogen-progestin hormone therapy for the treatment of hot flashes caused by hypoestrogenism. The effectiveness of progestin-only systemic hormone therapy for the treatment of hot flashes is much less studied and seldom is utilized in clinical practice. A small number of studies have reported that progestins, including micronized progesterone, medroxyprogesterone acetate, and norethindrone acetate, are effective treatment for hot flashes. Progestin-only systemic hormone therapy might be especially helpful for postmenopausal women with moderate to severe hot flashes who have a contraindication to estrogen treatment.

Micronized progesterone

Micronized progesterone (Prometrium) 300 mg daily taken at bedtime has been reported to effectively treat hot flashes in postmenopausal women. In one study, 133 postmenopausal women with an average age of 55 years and approximately 3 years from their last menstrual period were randomly assigned to 12 weeks of treatment with placebo or micronized progesterone 300 mg daily taken at bedtime.[1] Mean serum progesterone levels were 0.28 ng/mL (0.89 nM) and 27 ng/mL (86 nM) in the women taking placebo and micronized progesterone, respectively. Compared with placebo, micronized progesterone reduced daytime and nighttime hot flash frequency and severity. In addition, compared with placebo, micronized progesterone improved the quality of sleep.[1]

Most reviews conclude that micronized progesterone has minimal cardiovascular risk.[2] Micronized progesterone therapy might be especially helpful for postmenopausal women with moderate to severe hot flashes who have a contraindication to estrogen treatment such as those at increased risk for cardiovascular disease or women with a thrombophilia. Many experts believe that systemic estrogen therapy is contraindicated in postmenopausal women with an American Heart Association risk score greater than 10% over 10 years.[3] Additional contraindications to systemic estrogen include women with cardiac disease who have a thrombophilia, such as the Factor V Leiden mutation.[4]

For women who are at high risk for estrogen-induced cardiovascular events, micronized progesterone may be a better option than systemic estrogen for treating hot flashes. Alternatively, in these women at risk of cardiovascular disease a selective serotonin reuptake inhibitor, such as escitalopram, 10 mg to 20 mg daily, may be a good option for treating postmenopausal hot flashes.[5]

Medroxyprogesterone acetate

Medroxyprogesterone acetate, at a dosage of 20 mg daily, is an effective treatment for hot flashes. In a randomized clinical trial 27 postmenopausal women with hot flashes were randomly assigned to treatment with

placebo or medroxyprogesterone acetate 20 mg daily for 4 weeks. Vasomotor flushes were decreased by 26% and 74% in the placebo and medroxyprogesterone groups, respectively.[6]

Depot medroxyprogesterone acetate injections at dosages from 150 mg to 400 mg also have been reported to effectively treat hot flashes.[7,8] In a trial comparing the effectiveness of estrogen monotherapy (conjugated equine estrogen 0.6 mg daily) with progestin monotherapy (medroxyprogesterone acetate 10 mg daily), both treatments were equally effective in reducing hot flashes.[9]

Micronized progesterone vs medroxyprogesterone acetate

Experts in menopause medicine have suggested that in postmenopausal women micronized progesterone has a better pattern of benefits and fewer risks than medroxyprogesterone acetate.[10,11] For example, in the E3N observational study of hormones and breast cancer risk, among 80,377 French postmenopausal women followed for a mean of 8 years, the combination of transdermal estradiol plus oral micronized progesterone was associated with no significantly increased risk of breast cancer (relative risk [RR], 1.08, 95% confidence interval [CI], 0.89–1.31) compared with never users of postmenopausal hormone therapy.[12] By contrast, the combination of oral estrogen plus medroxyprogesterone acetate was associated with an increased risk of breast cancer (RR, 1.48; 95% CI, 1.02–2.16) compared with never users of postmenopausal hormone therapy. The E3N study indicates that micronized progesterone may have a more favorable breast health profile than medroxyprogesterone acetate.[12]

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Norethindrone acetate

Norethindrone acetate monotherapy is not commonly prescribed for the treatment of menopausal hot flashes. However, a large clinical trial has demonstrated that norethindrone acetate effectively suppresses hot flashes in women with endometriosis treated with depot leuprolide acetate (LA). In one trial 201 women with endometriosis were randomly assigned to 12 months of treatment with[13]:

- LA plus placebo pills
- LA plus norethindrone acetate (NEA) 5 mg daily
- LA plus NEA 5 mg daily plus conjugated equine estrogen (CEE) 0.625 mg daily, or
- LA plus NEA 5 mg daily plus CEE 1.25 mg daily.

The median number of hot flashes in 24 hours was 6 in the LA plus placebo group and 0 in both the LA plus NEA 5 mg daily group and the LA plus NEA 5 mg plus CEE 1.25 mg daily group. This study demonstrates that NEA 5 mg daily is an effective treatment for hot flashes.

In the same study, LA plus placebo was associated with a significant decrease in lumbar spine bone mineral density. No significant decrease in bone mineral density was observed in the women who received LA plus NEA 5 mg daily. This finding indicates that NEA 5 mg reduces bone absorption caused by hypoestrogenism. In humans, norethindrone is a substrate for the aromatase enzyme system.[14] Small quantities of ethinyl estradiol may be formed by aromatization of norethindrone in vivo,[15,16] contributing to the effectiveness of NEA in suppressing hot flashes and preserving bone density.

Progestin: The estrogen alternative to hot flashes

For postmenopausal women with moderate to severe hot flashes, estrogen treatment reliably suppresses hot flashes and often improves sleep quality and mood. For postmenopausal women with a contraindication to estrogen treatment, progestin-only treatment with micronized progesterone or norethindrone acetate may be an effective option. ●

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

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Breast cancer chemoprophylaxis in high-risk women: How persistent is the impact of an aromatase inhibitor after 5 years of use?

Among postmenopausal women at high risk for breast cancer N = 3,864), **those treated with anastrozole (N = 1,920) compared with placebo (N = 1,944) for 5 years had a 49% reduction in breast cancer** (85 vs 165 cases; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.39–0.66; *P*<.0001) **after a median follow-up of 131 months.** The reduction was larger in the first 5 years but remained significant after 5 years. Although the risk reduction from this endogenous estrogen-minimizing medication was persistent, no mortality benefit was observed.

Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395;117-122.

EXPERT COMMENTARY

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A manufacturer-sponsored trial initiated in 2003, IBIS-II (International Breast Cancer Intervention Study II) included 3,864 menopausal women (mean age at baseline, 59.4 years) at elevated risk for breast cancer. The women were randomly assigned to 5-year treatment with either placebo (N = 1,944) or the aromatase inhibitor anastrozole 1 mg daily (N = 1,920).[1]

Reporting on the long-term follow-up results of the trial, Cuzick and colleagues found that anastrozole use substantially reduced the incidence of all breast cancer, including invasive breast cancer and ductal carcinoma in situ. Key adverse events associated with anastrozole were fractures, arthralgias, and menopausal symptoms (vasomotor symptoms and vaginal dryness).

To determine whether anastrozole had any persistent impact, the investigators continued to follow participants for all breast cancers and other outcomes.[2]

Details of the study

This randomized controlled trial that included 3,864 postmenopausal women had

Dr. Kaunitz reports serving on advisory boards for Pfizer.

FAST TRACK

In a long-term follow-up of the IBIS-II trial, investigators found that anastrozole use substantially reduced the incidence of all breast cancer, including invasive breast cancer and ductal carcinoma in situ

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The breast cancer chemoprophylactic efficacy of anastrozole compares favorably with that of tamoxifen. Furthermore, in women with an intact uterus, the increased risks of gynecologic problems, including endometrial cancer, associated with tamoxifen do not occur with aromatase inhibitors. However, the lack of any obvious mortality benefit means the ultimate value of estrogen deprivation breast cancer chemoprophylaxis continues to be uncertain, especially given other risks, including bone loss. In view of these new data, it will be important for high-risk women considering aromatase inhibitor prophylaxis to understand that these medications have not been associated with a mortality benefit.

ANDREW M. KAUNITZ, MD, NCMP

a median overall follow-up of 131 months; the primary outcome was all breast cancer. Random assignment to anastrozole use (1,920 women) was associated with a 49% reduction in all breast cancer (85 cases vs 165 cases in the placebo group [N = 1,944]; HR, 0.51; 95% CI, 0.39–0.66; *P*<.0001).

In the first 5 years, risk reduction was 61% with anastrozole (*P*<.0001 for overall and the first 5 years of follow-up). Subsequently, the magnitude of the risk reduction attenuated to 37% (*P* = .014). With 12 years of follow-up, the estimated risk of being diagnosed with breast cancer was 8.8% and 5.3% in the placebo and anastrozole groups, respectively. The number needed to treat for 5 years to prevent 1 breast cancer was 29.

With anastrozole, prevention of estrogen–receptor positive tumors was substantially more robust at 54% (HR, 0.46; 95% CI, 0.33–0.65; *P*<.0001) than for estrogen–receptor negative tumors at 27% (HR, 0.77; 95% CI, 0.41–1.44; *P* = .41).

Over the course of the long-term study, the incidence of fractures and cardiovascular events was similar in the placebo and anastrozole groups. Arthralgias and menopausal symptoms were not assessed after the trial's initial 5 years. Overall, the number of deaths (all cause as well as breast cancer related) were similar in the placebo and anastrozole groups.

Study strengths and limitations

The authors noted that this updated analysis of the IBIS-II trial data offers further support for the use of anastrozole in breast cancer prevention for high-risk postmenopausal women. The extended posttreatment follow-up showed a significant continuing reduction in breast cancer, and there was no evidence of new late adverse effects. A limitation of the analysis, however, is that very few deaths from breast cancer occurred during the study timeframe. Thus, additional follow-up would be needed to assess anastrozole's effect on breast cancer mortality. ●

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The authors report no financial relationships relevant to this article.

ACOG guidelines on preconception genetic carrier screening, AI and embryo selection, and the hidden dangers of environmental toxicants and ways to mitigate them

Although we are not able to cover all of the important developments in fertility medicine over the past year, there were 3 important articles published in the past 12 months that we highlight here. First, we discuss an American College of Obstetricians and Gynecologists (ACOG) committee opinion on genetic carrier screening that was reaffirmed in 2019. Second, we explore an interesting retrospective analysis of time-lapse videos and clinical outcomes of more than 10,000 embryos from 8 IVF clinics, across 4 countries. The authors assessed whether a deep learning model could predict the probability of pregnancy with fetal heart from time-lapse videos in the hopes that their research can improve prioritization of the most viable embryo for single embryo transfer. Last, we consider a review of the data on obstetric and reproductive health effects of preconception and prenatal exposure to several environmental toxicants, including heavy metals, endocrine-disrupting chemicals, pesticides, and air pollution.

IN THIS ARTICLE

Preconception genetic carrier screening: Standardize your counseling approach

American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 690: carrier screening in the age of genomic medicine. Obstet Gynecol. 2017;129:e35–e40.

With the rapid development of advanced and high throughput platforms for DNA sequencing in the past several years, the cost of genetic testing has decreased dramatically. Women's health care providers in general, and fertility specialists in particular, are uniquely positioned to take advantage of these novel and yet affordable technologies by counseling prospective parents during the preconception counseling, or early prenatal period, about the availability of genetic carrier screening and

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The preconception period is the perfect time to have a discussion about genetic carrier screening; it offers the opportunity for timely interventions if desired by the couples or individuals.

its potential to provide actionable information in a timely manner. The ultimate objective of genetic carrier screening is to enable individuals to make an informed decision regarding their reproductive choices based on their personal values. In a study by Larsen and colleagues, the uptake of genetic carrier screening was significantly higher when offered in the preconception period (68.7%), compared with during pregnancy (35.1%), which highlights the significance of early counseling.[1]

FAST TRACK

The uptake of genetic carrier screening has been shown to be significantly higher when offered in the preconception period versus during pregnancy

Based on the Centers for Disease Control and Prevention's Birth/Infant Death Data set, birth defects affect 1 in every 33 (about 3%) of all babies born in the United States each year and account for 20% of infant mortality.[2] About 20% of birth defects are caused by single-gene (monogenic) disorders, and although some of these are due to dominant conditions or *de novo* mutations, a significant proportion are due to autosomal recessive, or X-chromosome linked conditions that are commonly assessed by genetic carrier screening.

ACOG published a committee opinion on "Carrier Screening in the Age of Genomic Medicine" in March 2017, which was reaffirmed in 2019.[3]

Residual risk. Several points discussed in this document are of paramount importance, including the need for pretest and posttest counseling and consent, as well as a discussion of "residual risk." Newer platforms employ sequencing techniques that potentially can detect most, if not all, of the disease-causing variants in the tested genes, such as the gene for cystic fibrosis and, therefore, have a higher detection rate compared with the older PCR-based techniques for a limited number of specific mutations included in the panel. Due to a variety of technical and biological limitations, however, such as allelic dropouts and the occurrence of *de novo* mutations, the detection rate is not 100%; there is always a residual risk that needs to be estimated and provided to individuals based on the existing knowledge on frequency of gene, penetrance of phenotype, and prevalence of condition in the general and specific ethnic populations.

Expanded vs panethnic screening. Furthermore, although sequencing technology has made "expanded carrier screening" for several hundred conditions, simultaneous to and independent of ethnicity and family history, more easily available and affordable, ethnic-specific and panethnic screening for a more limited number of conditions are still acceptable approaches. Having said this, when the first partner screened is identified to be a carrier, his/her reproductive partners must be offered next-generation sequencing to identify less common disease-causing variants.[4]

A cautionary point to consider when expanded carrier screening panels are requested is the significant variability among commercial laboratories with regard to the conditions included in their panels. In addition, consider the absence of a well-defined or predictable phenotype for some of the included conditions.

Perhaps the most important matter when it comes to genetic carrier screening is to have a standard counseling approach that is persistently followed and offers the opportunity for individuals to know about their genetic testing options and available reproductive choices, including the use of donor gametes, preimplantation genetic testing for monogenic disease (PGT-M, formerly known as preimplantation genetic diagnosis, or PGD), prenatal testing, and pregnancy management options. For couples and/or individuals who decide to proceed with an affected pregnancy, earlier diagnosis can assist with postnatal management.

Medicolegal responsibility. Genetic carrier screening also is of specific relevance to the field of fertility medicine and assisted reproductive technology (ART) as a potential liability issue. Couples and individuals who are undergoing fertility treatment with in vitro fertilization (IVF) for a variety of medical or personal reasons are a specific group that certainly should be offered genetic carrier screening, as they have the option of "adding on" PGT-M (PGD) to their existing treatment plan at a fraction of the cost and treatment burden that would have otherwise been needed if they were not undergoing IVF. After counseling, some individuals and couples may ultimately opt out of genetic carrier screening. The counseling discussion needs to be clearly documented in the medical chart.

Artificial intelligence and embryo selection

Tran D, Cooke S, Illingworth PJ, et al. Deep learning as a predictive tool for fetal heart pregnancy following time-lapse incubation and blastocyst transfer. Hum Reprod. 2019;34:1011-1018.

With continued improvements in embryo culture conditions and cryopreservation technology, there has been a tremendous amount of interest in developing better methods for embryo selection. These efforts are aimed at encouraging elective single embryo transfer (eSET) for women of all ages, thereby lowering the risk of multiple pregnancy and its associated adverse neonatal and obstetric outcomes—without compromising the pregnancy rates per transfer or lengthening the time to pregnancy.

One of the most extensively studied methods for this purpose is preimplantation genetic testing for aneuploidy (PGT-A, formerly known as PGS), but emerging data from large multicenter randomized clinical trials (RCTs) have again cast significant doubt on PGT-A's efficacy and utility.[5] Meanwhile, alternative methods for embryo selection are currently under investigation, including noninvasive PGT-A and morphokinetic assessment of embryo development via analysis of images obtained by time-lapse imaging.

The potential of time-lapse imaging

Despite the initial promising results from time-lapse imaging, subsequent RCTs have not shown a significant clinical benefit.[6] However, these early methods of morphokinetic assessment are mainly dependent on the embryologists' subjective assessment of individual static frames and "annotation" of observed spatial and temporal features of embryo development. In addition to being a very time-consuming task, this process is subject to significant interobserver and intraobserver variability.

Considering these limitations, even machine-based algorithms that incorporate these annotations along with such other clinical variables as parental age and prior obstetric history, have a low predictive power for the outcome of embryo transfer, with an area under the curve (AUC) of the ROC curve of 0.65 to 0.74. (An AUC of 0.5 represents completely random prediction and an AUC of 1.0 suggests perfect prediction.)[7]

A recent study by Tran and colleagues has employed a deep learning (neural network) model to analyze the entire raw time-lapse videos in an automated manner without prior annotation by embryologists. After analysis of 10,638 embryos from 8 different IVF clinics in 4 different countries,

FAST TRACK

Early use of time-lapse imaging for embryo selection has not shown clinical benefit, but early methods were dependent on embryologists' subjective assessment of features of embryo development

WHAT DOES THIS EVIDENCE MEAN FOR PRACTICE?

Improved standardization of noninvasive embryo selection with growing use of artificial intelligence is a promising new tool to improve the safety and efficacy of ART.

they have reported an AUC of 0.93 (95% confidence interval, 0.92–0.94) for prediction of fetal heart rate activity detected at 7 weeks of gestation or beyond. Although these data are very preliminary and have not yet been validated prospectively in larger datasets for live birth, it may herald the beginning of a new era for the automation and standardization of embryo assessment with artificial intelligence—similar to the rapidly increasing role of facial recognition technology for various applications.

Environmental toxicants: The hidden danger

Segal TR, Giudice LC. Before the beginning: environmental exposures and reproductive and obstetrical outcomes. Fertil Steril. 2019;112:613-621.

FAST TRACK

Environmental toxicant exposure has significant implications for fertility, infertility, pregnancy, perinatal health, childhood development, adult diseases, and later generational reproduction

We receive news daily about the existential risk to humans of climate change. However, a risk that is likely as serious goes almost unseen by the public and most health care providers. That risk is environmental toxicants.[8]

More than 80,000 chemicals are registered in the United States, most in the last 75 years. These chemicals are ubiquitous. All of us are continuously exposed to and suffused with these toxicants and their metabolites. Air pollution adds insult to injury. Since this exposure has especially significant implications for fertility, infertility, pregnancy, perinatal health, childhood development, adult diseases, and later generational reproduction, it is imperative that reproductive health professionals take responsibility for helping mitigate this environmental crisis.

The problem is exceptionally complicated

The risks posed by environmental toxicants are much less visible than those for climate change, so the public, policymakers, and providers are largely unaware or may even seem uncaring. Few health professionals have sufficient knowledge to deliver care in this area, know which questions to ask, or have adequate information/medical record tools to assist them in care—and what are the possible interventions?

Addressing risk posed by individual toxicants

Addressing the problem clinically requires asking patients questions about exposure and recommending interventions. Toxicant chemicals include the neurotoxin mercury, which can be addressed by limiting intake of fish, especially certain types.

Lead was used before 1978 in paint, it also was used in gas and in water pipes. People living in older homes may be exposed, as well as those in occupations exposed to lead. Others with lead exposure risk include immigrants from areas without lead regulations and people using pica- or lead-glazed pottery. Lead exposure has been associated with multiple pregnancy complications and permanently impaired intellectual development in children. If lead testing reveals high levels, chelation therapy can help.

Cadmium is a heavy metal used in rechargeable batteries, paint pigment, and

plastic production. Exposure results from food intake, smoking, and second-hand smoke. Cadmium accumulates in the liver, kidneys, testes, ovaries, and placenta. Exposure causes itai-itai disease, which is characterized by osteomalacia and renal tubular dysfunction as well as epigenetic changes in placental DNA and damage to the reproductive system. Eating organic food and reducing industrial exposure to cadmium are preventive strategies.

Pesticides are ubiquitous, with 90% of the US population having detectable levels. Exposure during the preconception period can lead to intrauterine growth restriction, low birth weight, subsequent cancers, and other problems. Eating organic food can reduce risk, as can frequent hand washing when exposed to pesticides, using protective gear, and removing shoes in the home.

Endocrine-disrupting chemicals (EDCs) are chemicals that can mimic or block endogenous hormones, which leads to adverse health outcomes. In addition to heavy metals, 3 important EDCs are bisphenol A (BPA), phthalates, and polybrominated diethyl ethers (PBDEs). Exposure is ubiquitous from industrial food processing, personal care products, cosmetics, and dust. Phthalates and BPA have short half-lives of hours to days, while PBDEs can persist in adipose tissue for months. Abnormal urogenital and neurologic development and thyroid disruption can result. Eating organic food, eating at home, and decreasing processed food intake can reduce exposure.

BPA is used in plastics, canned food liners, cash register receipts, and epoxy resins. Exposure is through inhalation, ingestion, and dermal absorption and affects semen quality, fertilization, placentation, and early reproduction. Limiting the use of plastic containers, not microwaving food in plastic, and avoiding thermal paper cash register receipts can reduce exposure.

Phthalates are synthetically derived and used as plasticizers in personal and medical products. The major source of phthalate exposure is food; exposure causes sperm, egg, and DNA damage. Phthalate avoidance involves replacing plastic bottles with glass or stainless steel, avoiding reheating food in plastic containers, and choosing "fragrance free" products.

PBDEs are used in flame retardants on upholstery, textiles, carpeting, and some electronics. Most PBDEs have been replaced by alternatives; however, their half-life is up to 12 years. Complications caused by PBDEs include thyroid disruption, resulting in abnormal fetal brain development. Avoiding dust and furniture that contain PBDEs, as well as hand washing, reduces exposure risk.

Air pollutants are associated with adverse obstetric outcomes and lower cognitive function in children. Avoiding areas with heavy traffic, staying indoors when air is heavily polluted, and using a HEPA filter in the home can reduce chemicals from air pollution.

CONTINUED ON PAGE 16

TABLE 1 Environmental toxicants

- Mercury
- Lead
- Cadmium
- Pesticides
- Endocrine-disrupting chemicals
  - Bisphenol A
  - Phthalates
  - Polybrominated diethyl ethers
- Air pollution

TABLE 2 General interventions to reduce environmental toxicants exposure

1. Limit certain types of fish intake
2. Increase organic foods, decrease processed food, eat at home
3. Replace plastic containers/bottles with glass or stainless steel
4. Do not microwave in plastic
5. Choose personal care products and cosmetics carefully, fragrance-free
6. Remove shoes in home, avoid dust
7. Reduce exposure to industrial toxicants, furniture with polybrominated diethyl ethers
8. Wash hands when exposed to pesticides, other toxicants
9. Avoid thermal paper cash register receipts
10. Avoid heavy traffic areas, stay indoors when air is polluted, use HEPA filter in home

CONTINUED FROM PAGE 15

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Environmental toxicants are a significant health problem that can be effectively mitigated through patient questions and recommended interventions.

Recommendations

The magnitude of the problem that environmental toxicant exposure creates requires health care providers to take action. The table in the publication by Segal and Giudice can be used as a tool that patients can answer first themselves before review by their provider.[2] It can be added to your electronic health record and/or patient portal. Even making general comments to raise awareness, asking questions regarding exposure, and making recommendations can be helpful (**TABLES 1 AND 2,** page 15). When possible, we also should advocate for public awareness and policy changes that address this significant health issue. ●

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Émile Zola

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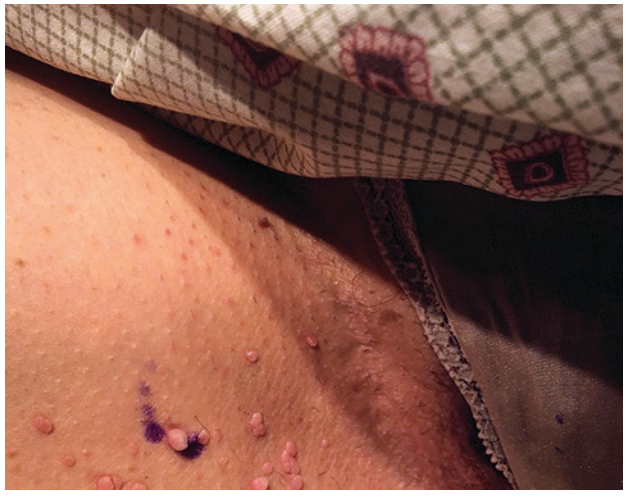
Can you identify these numerous papules in the groin area?

A case of multiple asymptomatic "pink skin tags"

Penelope J. Kallis, MD; Stephanie J. Carstens, MD; and Andrew M. Kaunitz, MD, NCMP

FIGURE 1 Pink papules



Multiple smooth, flat-topped, pedunculated pink papules on the right upper medial thigh. The biopsied lesion is marked with gentian violet.

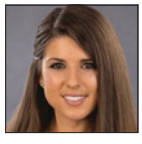
CASE Skin tags on the groin

A 47-year-old woman with no personal history of skin cancer presents to a dermatologist for annual skin surveillance examination. She notes multiple "pink skin tags" on the groin, present for 4 months. She says they are asymptomatic and have not been treated previously. She states that she is in a long-term monogamous relationship. Physical examination reveals multiple smooth, flat-topped, pedunculated pink papules on the bilateral upper inner thighs. Shave biopsy of a lesion on the right upper medial thigh is performed to aid in diagnosis (**FIGURE 1**).

Biopsy is most likely to reveal which of the following diagnoses?

- Acrochordons
- Condylomata acuminata
- Mollusca contagiosa

Turn to page 24 to see if you are correct



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The authors report no financial relationships relevant to this article.

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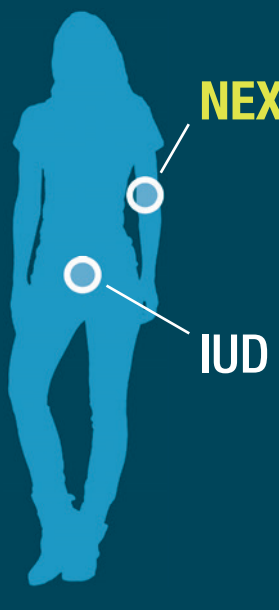

Help your patients understand both of their LARC location options[1]

IUD, intrauterine device; LARC, long-acting reversible contraceptive.

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

- NEXPLANON should not be used in women who have known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; liver tumors, benign or malignant, or active liver disease; undiagnosed abnormal genital bleeding; known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past; and/or allergic reaction to any of the components of NEXPLANON.

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.
- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.
- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.
- **Rule out pregnancy before inserting NEXPLANON.**

Educate her about the risk of serious vascular events

- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events [stroke and myocardial infarction (MI)] or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis (DVT), retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using etonogestrel implants have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.

US-XPL-00588 05/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Up to **3 years** of pregnancy prevention*

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

*NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.

†Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

- Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum.
- Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Consider removing the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Counsel her about changes in bleeding patterns

- Women are likely to have changes in their menstrual bleeding pattern with NEXPLANON, including changes in frequency, intensity, or duration. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, changes in bleeding pattern were the most common reason reported for stopping treatment (11.1%). Counsel women regarding potential changes they may experience.

Be aware of other serious complications, adverse reactions, and drug interactions

- Remove NEXPLANON if jaundice occurs.
- Remove NEXPLANON if blood pressure rises significantly and becomes uncontrolled.
- Prediabetic and diabetic women using NEXPLANON should be carefully monitored.
- Carefully observe women with a history of depressed mood. Consider removing NEXPLANON in patients who become significantly depressed.
- The most common adverse reactions (≥10%) reported in clinical trials were headache (24.9%), vaginitis (14.5%), weight increase (13.7%), acne (13.5%), breast pain (12.8%), abdominal pain (10.9%), and pharyngitis (10.5%).
- Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the effectiveness of NEXPLANON or increase breakthrough bleeding.
- The efficacy of NEXPLANON in women weighing more than 130% of their ideal body weight has not been studied. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. Therefore, NEXPLANON may be less effective in overweight women.
- Counsel women to contact their health care provider immediately if, at any time, they are unable to palpate the implant.
- NEXPLANON does not protect against HIV or other STDs.

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol.* 2017;130(5):e251–e269.

MERCK

Nexplanon®
(etonogestrel implant) 68mg

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

Women should be informed that this product does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver tumors, benign or malignant, or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past
- Allergic reaction to any of the components of NEXPLANON *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

The following information is based on experience with the etonogestrel implants (IMPLANON® [etonogestrel implant] and/or NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.

Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

If at any time the implant cannot be palpated, it should be localized and removal is recommended.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

Changes in Menstrual Bleeding Patterns

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use*

Bleeding Patterns	Definitions	%†
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting more than 14 days in 90 days	17.7
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

† % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

Ectopic Pregnancies

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasion, surgery may be required.

Carcinoma of the Breast and Reproductive Organs

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive *[see Contraindications]*. Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings. Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops. Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON. The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated *[see Contraindications]*.

Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

Elevated Blood Pressure

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

Carbohydrate and Lipid Metabolic Effects

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON. Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

Depressed Mood

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

Fluid Retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

Contact Lenses
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration].*

Monitoring
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

Drug-Laboratory Test Interactions
Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS
In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).
Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Bleeding Irregularities*	11.1%
Emotional Lability†	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression‡	1.0%

*Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
† Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
‡ Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Headache	24.9%
Vaginitis	14.5%
Weight increase	13.7%
Acne	13.5%
Breast pain	12.8%
Abdominal pain	10.9%
Pharyngitis	10.5%
Leukorrhea	9.6%
Influenza-like symptoms	7.6%
Dizziness	7.2%
Dysmenorrhea	7.2%
Back pain	6.8%
Emotional lability	6.5%
Nausea	6.4%
Pain	5.6%
Nervousness	5.6%
Depression	5.5%
Hypersensitivity	5.4%
Insertion site pain	5.2%

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives
Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.
Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase the serum concentrations of progestins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efavirenz] or increase [e.g., etravirene]). These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs
Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporine) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant *[see Contraindications].* Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.

Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers.This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

Pediatric Use
Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

Geriatric Use
This product has not been studied in women over 65 years of age and is not indicated in this population.

Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications].*

Overweight Women
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE
Overdosage may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY
In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*
- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.
- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other STDs.
- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

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Condylomata acuminata

Condylomata acuminata (CA), or anogenital warts, are the cutaneous manifestation of infection by human papillomavirus (HPV). The virus is transmitted primarily via sexual contact with infected skin or mucosa, although it also may result from nonsexual contact or vertical transmission during vaginal delivery.[1] More than 200 types of HPV have been identified; however, genotypes 6 and 11 are most commonly implicated in the development of CA and are associated with a low risk for oncogenesis. Nevertheless, CA pose a tremendous economic and psychological burden on the health care system and those affected, respectively, representing the most common sexually transmitted viral disease in the United States.[2]

Clinical presentation

CA present as discrete or clustered smooth, papillomatous, sessile, exophytic papules or plaques, often lacking the thick, horny scale seen in common warts, and they may be broad based or pedunculated.[2] The anogenital region is affected, including the external genitalia, perineum, perianal area, and adjacent skin such as the mons pubis and inguinal folds. Extension into the urethra or vaginal, cervical, and anal canals is possible, although rarely beyond the dentate line.[2,3] Lesions typically are asymptomatic but may be extensive or disfiguring, often noticed by patients upon self-inspection and leading to significant distress. Symptoms such as pruritus, pain, bleeding, or discharge may develop in traumatized or secondarily infected lesions.[1,3]

Diagnosis

Although CA can be diagnosed clinically, biopsy facilitates definitive diagnosis in less clear-cut cases.[1,3] Histologically, CA are characterized by hyperkeratosis, parakeratosis, acanthosis, and papillomatosis, with the presence of koilocytes in the epidermis.[2]

Treatment

Treatment of CA is challenging, as there are currently no antiviral therapies available to cure the condition. Treatment options include destructive, immunomodulatory, and antiproliferative therapies, either alone or in combination. There is no first-line therapy indicated for CA, and treatment selection is dependent on multiple patient-specific factors, including the size, number, and anatomic location of the lesions, as well as ease of treatment and adverse effects.[2]

Topical therapies. For external CA, there are several treatments that may be applied by patients themselves, including topical podophyllotoxin, imiquimod, and sinecatechins (**TABLE**).[1] Podophyllotoxin (brand name Condylox) is an antiproliferative agent available as a 0.15% cream or 0.5% solution.[1,2] It should be applied twice daily for 3 consecutive days per week for up to 4 weeks. Podophyllotoxin is contraindicated in pregnancy and may cause local irritation.[2]

TABLE Estimated cost of patient-applied medications for anogenital warts

Medication (Brand name)	Cost[a]
Condylox	$23
Aldara	$17
Zyclara	$509
Veregen	$1326

[a]According to GoodRx.com. With variations in insurance formularies and coupon programs online, actual cost to patient may not be what is reflected on GoodRx.com.

Imiquimod (brand names Aldara and Zyclara) is an immunomodulatory, available as a 5% and 3.75% cream. For external genital warts, the cream should be applied 3 times per week for up to 16 weeks; for perianal warts it should be applied daily for up to 8 weeks. Adverse effects of imiquimod include local irritation and systemic flu-like symptoms and are prominent with the 3.75% formulation, reducing adherence.[1,2,4]

Sinecatechins (brand name Veregen; 10% or 15% ointment) is an active ingredient in green tea and has reported antioxidant, antiviral, and antitumor properties. It is applied 3 times daily for up to 16 weeks.[2,4] Local reactions may occur and, rarely, severe reactions such as vulvovaginitis and pelvic pain, have been reported in women.[2,4]

In-office treatment options include cryotherapy, trichloroacetic acid (TCA), intralesional immunotherapy, laser therapy, phototherapy, and surgical options.[2] Liquid nitrogen is cost-effective, efficacious, and safe for use in pregnancy; it is used in 2 to 3 freeze/thaw cycles per cryotherapy session to induce cellular damage.[1,2] Its disadvantages include adverse effects, such as blistering, ulceration, dyspigmentation, and scarring. In addition, subclinical lesions in adjacent skin are not addressed during treatment.[2]

TCA is a caustic agent applied in the office once weekly or every 2 to 3 weeks for a maximum of 3 to 4 months, with similar benefits to cryotherapy in terms of ease of application and safety in pregnancy. There is the risk of blistering and ulceration in treated lesions as well as in inadvertently treated adjacent skin.[1]

Intralesional immunotherapy with *Candida* antigen (brand name Candin) is used in 3 sessions 4 to 6 weeks apart and is safe, with minimal adverse effects.[2]

Laser therapy treatment options include carbon dioxide laser therapy and ND:YAG laser. Their use is limited, however, by availability and cost.[1,2]

CA may be removed surgically via shave excision, scissor excision, curettage, and electrosurgery. These procedures can be painful, however, requiring local anesthesia and having a prolonged healing course.[1,2]

CA recurrence

CA unfortunately has a high rate of recurrence despite treatment, and patients require extensive counseling. Patients should be screened for other sexually transmitted infections and advised to notify their sexual partners. If followed properly, safe sexual practices, including condom use and limiting sexual partners, may prevent further transmission.[1] The quadrivalent HPV vaccine (effective for the prevention of infection with HPV genotypes 6, 11, 16, and 18 in unexposed individuals) is ineffective in treating patients with pre-existing CA but can protect against the acquisition of other HPV genotypes included in the vaccine.[1,5]

Arriving at the diagnosis

Acrochordons are a common skin finding in the groin, but the onset is more gradual and the individual lesions tend to be more pedunculated. Molluscum is also on the differential and can affect the genitalia. Molluscum lesions have a characteristic central dimple or dell, which is absent in CA.

CASE Treatment course

The patient was treated with successive sessions of cryotherapy in combination with a course of topical imiquimod followed by several injections with Candida antigen, with persistence of some lesions as well as recurrence. ●

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COMMENTARY

Should supplemental MRI be used in otherwise average-risk women with extremely dense breasts?

Recent data show that supplemental MRI screening in women with extremely dense breasts and negative screening mammograms decreases the rate of interval breast cancers. It remains unclear, however, whether supplemental MRIs will improve other outcomes, such as breast cancer mortality.

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While the frequency of dense breasts decreases with age, approximately 10% of women in the United States have extremely dense breasts (Breast Imaging, Reporting, and Data System [BI-RADS] category D), and another 40% have heterogeneously dense breasts (BI-RADS category C).[1] Women with dense breasts have both an increased risk for developing breast cancer and reduced mammographic sensitivity for breast cancer detection compared with women who have nondense breasts.[2]

These 2 observations have led the majority of states to pass legislation requiring that women with dense breasts be informed of their breast density, and most require that providers discuss these results with their patients. Thoughtful clinicians who review the available literature, however, will find sparse evidence on which to counsel patients as to next steps.

Now, a recent trial adds to our knowledge about supplemental magnetic resonance imaging (MRI) breast screening in women with extremely dense breasts.

DENSE trial offers high-quality data

Bakker and colleagues studied women aged 50 to 74 who were participating in a Netherlands population-based biennial mammography screening program.[3] They enrolled average-risk women with extremely dense breasts who had a negative screening digital mammogram into the Dense Tissue and Early Breast Neoplasm Screening (DENSE) multicenter trial. The women were randomly assigned to receive either continued biennial digital mammography or supplemental breast MRI.

The primary outcome was the between-group difference in the development of interval breast cancers—that is, breast cancers detected by women or their providers between rounds of screening mammography. Interval breast cancers were chosen as the primary outcome for 2 reasons:

- interval cancers appear to be more aggressive tumors than those cancers detected by screening mammography
- interval cancers can be identified over a shorter time interval, making them easier to study than outcomes such as breast cancer mortality, which typically require more than a decade to identify.

The DENSE trial's secondary outcomes included recall rates from

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TABLE 1 Interval cancer rates in the mammography-only group vs the supplemental MRI group[3]

	Mammography-only group	MRI-assigned group	If all had MRI[a]
Interval cancer per 1,000 screenings (95% CI)	5.0 (4.3–5.8)	2.5 (1.6–3.8)	0.8
Difference in interval cancer compared with mammography only (95% CI)	— (reference)	-2.5 (1.0–3.7)	-4.2 (2.0–6.4)

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging.

[a]Calculated using CACE (complier average causal effect) analysis estimating the effect of all women undergoing supplemental MRI.

TABLE 2 Tumor characteristics in women who had mammography only vs supplemental MRI[3]

	Breast cancers detected on MRI	Interval cancers in women who had MRI	Interval cancers in women who were assigned to but did not have MRI	Interval cancers in women who had mammography only
Median size, mm	9.5	13	15	17
Percent (N) early stage (stage 0, I)	91.1 (72)	50 (2)	50 (8)	41.6 (67)
Percent (N) late stage (stage II–IV)	9 (7)	50 (2)	50 (8)	58.4 (94)

Abbreviation: MRI, magnetic resonance imaging.

MRI, cancer detection rates on MRI, positive predictive value of MRIs requiring biopsy, and breast cancer characteristics (size, stage) diagnosed in the different groups.

Between-group difference in incidence of interval cancers

A total of 40,373 women with extremely dense breasts were screened; 8,061 of these were randomly assigned to receive breast MRI and 32,312 to continued mammography only (1:4 cluster randomization) across 12 mammography centers in the Netherlands. Among the women assigned to the MRI group, 59% actually underwent MRI (4,783 of the 8,061).

The interval cancer rate in the mammography-only group was 5.0 per 1,000 screenings (95% confidence interval [CI], 4.3–5.8), while the interval cancer rate in the MRI-assigned group was 2.5 per 1,000 screenings (95% CI, 1.6–3.8) (**TABLE 1**).[3]

Key secondary outcomes

Of the women who underwent supplemental MRI, 9.49% were recalled for additional imaging, follow-up, or biopsy. Of the 4,783 women who had an MRI, 300 (6.3%) underwent a breast biopsy, and 79 breast cancers (1.65%) were detected. Sixty-four of these cancers were invasive, and 15 were ductal carcinoma in situ (DCIS). Among women who underwent a biopsy for an MRI-detected abnormality, the positive predictive value was 26.3%.

Tumor characteristics. For women who developed breast cancer during the study, both tumor size at diagnosis and tumor stage (early vs late) were described. **TABLE 2** shows these results in the women who had their breast cancer detected on MRI, those in the MRI-assigned group who developed interval cancer, and those in the mammography-only group who had interval cancers.[3] Overall, tumor size was smaller in the interval group who underwent MRI compared with those who underwent mammography only.

Study contributes valuable data, but we need more on long-term outcomes

The trial by Bakker and colleagues employed a solid study design as women were randomly assigned to supplemental MRI screening or ongoing biennial mammography,

and nearly all cancers were identified in the short-term of follow-up. In addition, very few women were lost to follow-up, and secondary outcomes, including false-positive rates, were collected to help providers and patients better understand some of the potential downsides of supplemental screening.

The substantial reduction in interval cancers (50% in the intent-to-screen analysis and 84% in the women who actually underwent supplemental MRI) was highly statistically significant ($P<.001$). While there were substantially fewer interval cancers in the MRI-assigned group, the interval cancers that did occur were of similar stage as those in the women assigned to the mammography-only group (TABLE 2).

Data demonstrate that interval cancers appear to be more aggressive than screen-detected cancers.[4] While reducing interval cancers should be a good thing overall, it remains unproven that using supplemental MRI in all women with dense breasts would reduce breast cancer specific mortality, all-cause mortality, or the risk of more invasive treatments (for example, the need for chemotherapy or requirement for mastectomy).

On the other hand, using routine supplemental breast MRI in women with extremely dense breasts would result in very substantial use of resources, including cost, radiologist time, provider time, and machine time. In the United States, approximately 49 million women are aged 50 to 74.[5] Breast MRI charges commonly range from $1,000 to $4,000. If the 4.9 million women with extremely dense breasts underwent supplemental MRI this year, the approximate cost would be somewhere between $4.9 and $19.5 billion for imaging alone. This does not include callbacks, biopsies, or provider time for ordering, interpreting, and arranging for follow-up.

While the reduction in interval cancers seen in this study is promising, more assurance of improvement in important outcomes—such as reduced mortality or reduced need for more invasive breast cancer treatments—should precede any routine change in practice.

Unanswered questions

This study did not address a number of other important questions, including:

Should MRI be done with every round of breast cancer screening given the possibility of prevalence bias? Prevalence bias can be defined as more cancers detected in the first round of MRI screening with possible reduced benefit in future rounds of screening. The study authors indicated that they will continue to analyze the study results to see what occurs in the next round of screening.

Is there a similar impact on decreased interval cancers in women undergoing annual mammography or in women screened between ages 40 and 49? This study was conducted in women aged 50 to 74 undergoing mammography every 2 years. In the United States, annual mammography in women aged 40 to 49 is frequently recommended.

What effect does supplemental MRI screening have in women with heterogeneously dense breasts, which represents 40% of the population? The US Food and Drug Administration recommends that all women with dense breasts be counseled regarding options for management.[6]

Do these results translate to the more racially and ethnically diverse populations of the United States? In the Netherlands, where this study was conducted, 85% to 90% of women are either Dutch or of western European origin. Women of different racial and ancestral backgrounds have biologically different breast cancers and cancer risk (for example, higher rates of triple-negative breast cancers in African American women; 10-fold higher rates of *BRCA* pathogenic variants in Ashkenazi Jewish women).

Use validated tools to assess risk comprehensively

Women aged 50 to 74 with extremely dense breasts have reduced interval cancers following a normal biennial mammogram if supplemental MRI is offered, but the long-term benefit of identifying these cancers earlier is unclear. Until more data are available on important long-term outcomes (such as breast cancer mortality and need for more invasive treatments), providers should consider breast density in the context of a more comprehensive assessment of breast cancer risk using a validated breast cancer risk assessment tool.

I prefer the modified version of the International Breast Cancer Intervention Study (IBIS) tool, which is readily available online (https://ibis.ikonopedia.com/).[7] This tool incorporates several breast cancer risk factors, including reproductive risk factors, body mass index, *BRCA* gene status, breast density, and family history. The tool takes 1 to 2 minutes to complete and provides an estimate of a woman's 10-year risk and lifetime risk of breast cancer.

If the lifetime risk exceeds 20%, I offer the patient supplemental MRI screening, consistent with current recommendations of the National Comprehensive Cancer Network and the American Cancer Society.[8,9] I generally recommend starting breast

imaging screening 7 to 10 years prior to the youngest breast cancer occurrence in the family, with mammography starting no earlier than age 30 and MRI no earlier than age 25. Other validated tools also can be used.[10-13]

Incorporating breast density and other important risk factors allows a more comprehensive analysis upon which to counsel women about the value (benefits and harms) of breast imaging.[8]

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RISKY MEDICINE, PART 2

ObGyn malpractice liability risk: 2020 developments and probabilities

Paid medical malpractice claims have trended downward in recent decades. Why?

Steven R. Smith, MS, JD, and Joseph S. Sanfilippo, MD, MBA

In this second in a series of 3 articles discussing medical malpractice and the ObGyn we look at the reasons for malpractice claims and liability, what happens to malpractice claims, and the direction and future of medical malpractice. The first article dealt with 2 sources of major malpractice damages: the "big verdict" and physicians with multiple malpractice paid claims. Next month we look at the place of apology in medicine, in cases in which error, including negligence, may have caused a patient injury.

IN THIS ARTICLE

CASE 1 Long-term brachial plexus injury

Right upper extremity injury occurs in the neonate at delivery with sequela of long-term brachial plexus injury (which is diagnosed around 6 months of age). Physical therapy and orthopedic assessment are rendered. Despite continued treatment, discrepancy in arm lengths (ie, affected side arm is noticeably shorter than opposite side) remains. The child cannot play basketball with his older brother and is the victim of ridicule, the plaintiff's attorney emphasizes. He is unable to properly pronate or supinate the affected arm.

The defendant ObGyn maintains that there was "no shoulder dystocia [at delivery] and the shoulder did not get obstructed in the pelvis; shoulder was delivered 15 seconds after delivery of the head." The nursing staff testifies that if shoulder dystocia had been the problem they would have launched upon a series of procedures to address such, in accord with the delivering obstetrician. The defense expert witness testifies that a brachial plexus injury can happen without shoulder dystocia.

A defense verdict is rendered by the Florida jury.[1]

CASE 2 Shoulder dystocia

During delivery, the obstetrician notes a shoulder dystocia ("turtle sign"). After initial attempts to release the shoulder were unsuccessful, the physician applies traction several times to the head of the child, and the baby is delivered. There is permanent injury to the right brachial plexus. The defendant ObGyn says that traction was necessary to dislodge the shoulder, and that the injury was the result of the forces of labor (not the traction). The expert witness for

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The authors report no financial relationships relevant to this article.

the plaintiff testifies that the medical standard of care did not permit traction under these circumstances, and that the traction was the likely cause of the injury.

The Virginia jury awards $2.32 million in damages.[2]

Note: The above vignettes are drawn from actual cases but are only outlines of those cases and are not complete descriptions of the claims in the cases. Because the information comes from informal sources, not formal court records, the facts may be inaccurate and incomplete. They should be viewed as illustrations only.

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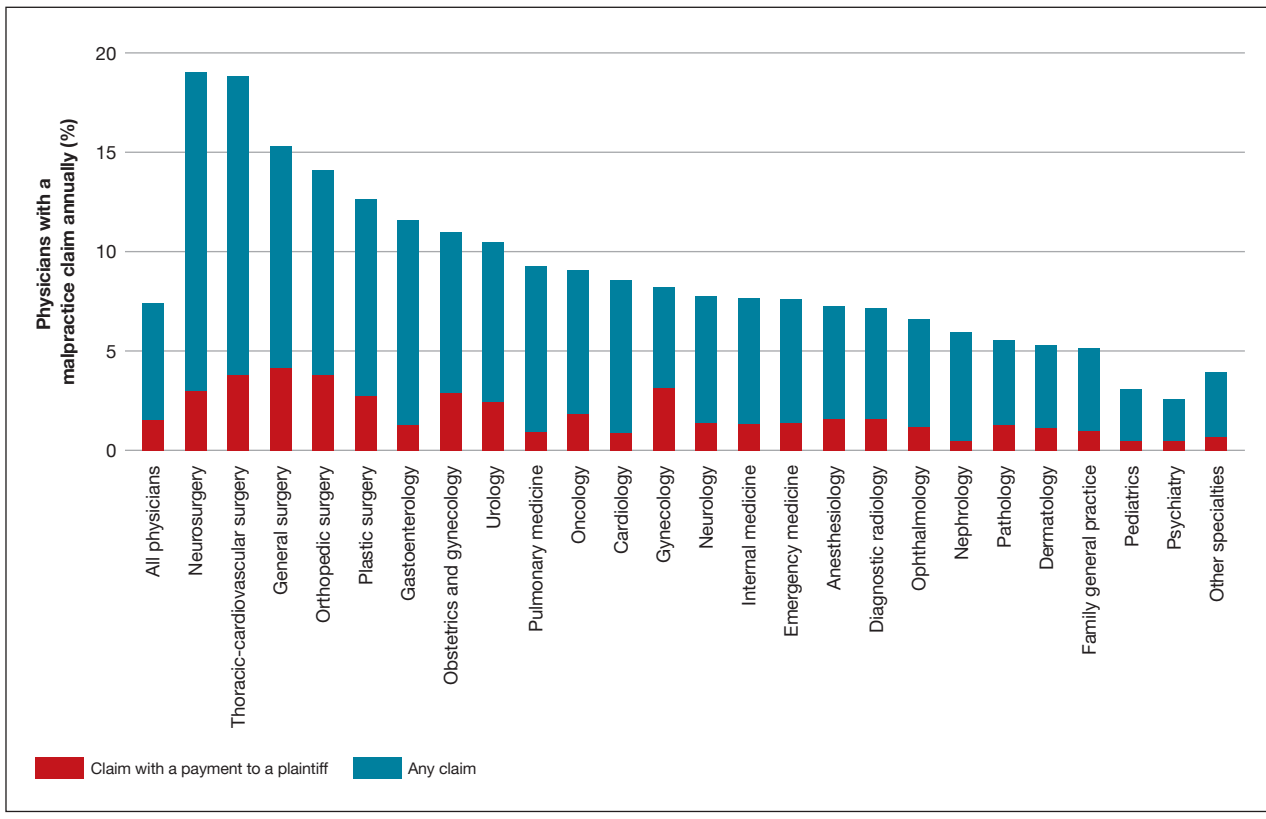
The trend in malpractice

It has been clear for many years that medical malpractice claims are not randomly or evenly distributed among physicians. Notably, the variation among specialties has, and continues to be, substantial (**FIGURE 1**).[3] Recent data suggest that, although paid claims per "1,000 physician-years" averages 14 paid claims per 1,000 physician years, it ranges from 4 or 5 in 1,000 (psychiatry and pediatrics) to 53 and 49 claims per 1,000 (neurology and plastic surgery, respectively). Obstetrics and gynecology has the fourth highest rate at 42.5 paid claims per 1,000 physician years.[4] (These data are for the years 1992–2014.)

FIGURE 1 **Medical malpractice by specialty**[3]



Percentage of physicians facing a malpractice claim (with and without payment to a plaintiff) annually, according to specialty (1991–2005).

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FIGURE 2 Annual rates of paid settlements[6]

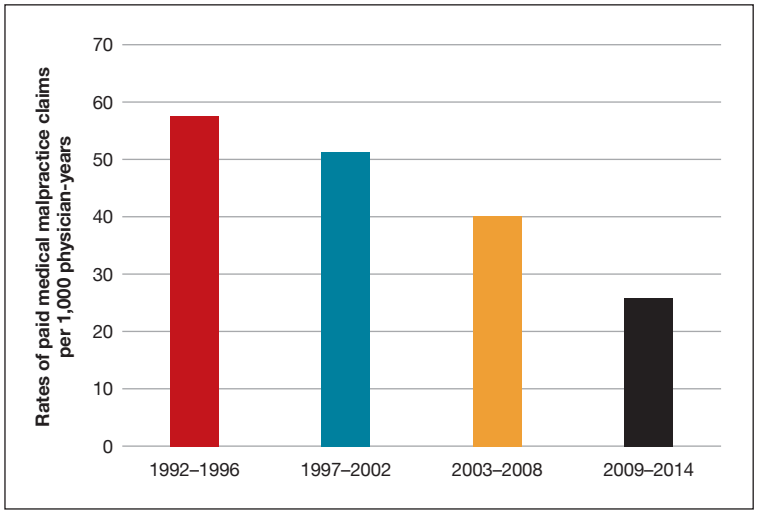

FIGURE 3 ObGyn medical professional liability insurance premiums for $1M/$3M policies, selected insurers, 2008 and 2017[a,7]

Area of country	2008	2017
California (Los Angeles, Orange)	$63,272	$49,804
Connecticut	$170,389	$170,389
Florida (Miami, Dade)	$238,728	$190,829
Illinois (Cook, Madison, St. Clair)	$178,921	$177,441
New Jersey	$117,340	$90,749
New York (Nassau, Suffolk)	$194,935	$214,999
Pennsylvania (Philadelphia)	$171,813	$119,466

[a]The data are based on Annual Rate Survey (October) Issues of the Medical Liability Monitor, 2008–2017. The numbers are manual premiums reported by a liability insurer selected on the basis of data availability in every year. Premiums reported for Connecticut pertain to $1 million/$4 million limits, and Pennsylvania premiums include Patient Compensation Fund surcharges.

[b]Counties to which the premiums refer are in parentheses. Counties in California (CA), Illinois (IL), and Pennsylvania (PA) changed slightly over time. However, CA counties always include Los Angeles, IL counties always include Cook, and PA counties always include Philadelphia.

The number of ObGyn paid malpractice claims has decreased over time. Although large verdicts and physicians with multiple paid malpractice claims receive a good deal of attention (as we noted in part 1 of our series), in fact, paid medical malpractice claims have trended downward in recent decades.[5] When the data above are disaggregated by 5-year periods, for example, in obstetrics and gynecology, there has been a consistent reduction in paid malpractice claims from 1992 to 2014. Paid claims went from 58 per 1,000 physician-years in 1992–1996 to 25 per 1,000 in 2009–2014 (**FIGURE 2**).[4,6] In short, the rate dropped by half over approximately 20 years.[4]

It is reasonable to expect that such a decline in the cost of malpractice insurance premiums would follow. Robert L. Barbieri, MD, who practices in Boston, Massachusetts, in his excellent recent editorial in OBG MANAGEMENT[6] reported that his professional liability insurance premiums decreased 18% from 2014 to 2019, and his colleague reported a 22% reduction during the same time period.[6] An American Medical Association report of 7 states or metropolitan areas for 2008 to 2017 found considerable variance. The study looked at the rates and the trend of rates for malpractice insurance in several areas of the United States (**FIGURE 3**).[7] For ObGyns, one of these jurisdictions experienced increased rates; in one other, rates stayed the same, and in 5 jurisdictions, the rates went down. The premiums varied across the country, however. In 2017, Los Angeles/Orange had an average rate of $49,804, and in Nassau and Suffolk counties, New York, the rate was $214,999. The median rate was approximately $170,000.[7]

Why have malpractice payouts declined overall?

Have medical errors declined?

It would be wonderful if the reduction in malpractice claims represented a significant decrease in medical errors. Attention to medical errors was driven by the first widely noticed study of medical error deaths. The Institute of Medicine (IOM) study in 2000, put the number of deaths annually at 44,000

CONTINUED ON PAGE 34

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TABLE 1. Health-system level medical error-reduction strategies for ObGyn practice[6]

- Elective induction bundle focused on safe use of oxytocin
- Augmentation bundle focused on early intervention for possible fetal metabolic acidosis
- Operative vaginal delivery bundle
- TeamSTEPPS teamwork training to improve communication quality
- Best practices education with focus on electronic fetal monitoring
- Regular performance feedback to hospitals and clinicians
- Implementation of quality improvement collaboration to support error-reduction interventions
- 24-hour in-house physician coverage of an obstetrics service
- Conservative approach to trial of labor after a prior cesarean delivery
- Utilization of a comprehensive, standardized event note in cases of a shoulder dystocia
- Judicious use of oxytocin, misoprostol, and magnesium sulfate
- Systematic improvement in quality of communication among physicians and nurses through the use of team training, preprocedure huddles, and time-out processes
- Rapid response systems to rescue hospital patients with worrisome vital signs
- Standardized responses to a worrisome category 2 or 3 fetal heart rate tracing
- Rapid recognition, evaluation, and treatment of women with hemorrhage, severe hypertension, sepsis, and venous thromboembolism
- Identification and referral of high-risk patients to tertiary centers
- Closed loop communication of critical imaging and laboratory results
- Universal insurance coverage for health care, including contraception, obstetrics, and pediatric care

to 98,000.[8] There have been many efforts to reduce such errors, and it is possible that those efforts have indeed reduced errors somewhat.[4] Barbieri provided a helpful digest of many of the error-reduction suggestions for ObGyn practice (**TABLE 1**).[6] But the number of medical errors remains high. More recent studies have suggested that the IOM's reported number of injuries may have been low.[9] In 2013, one study suggested that 210,000 deaths annually were "associated with preventable harm" in hospitals. Because of how the data were gathered the authors estimated that the actual number of preventable deaths was closer to 400,000 annually. Serious harm to patients was estimated at 10 to 20 times the IOM rate.[9]

Therefore, a dramatic reduction in preventable medical errors does not appear to explain the reduction in malpractice claims. Some portion of it may be explained by malpractice reforms—discussed on page 36.

The collective accountability factor

The way malpractice claims are paid (**FIGURE 4**, page 36),[10] reported, and handled may explain some of the apparent reduction in overall paid claims. Perhaps the advent of "collective accountability," in which patient care is rendered by teams and responsibility accepted at a team level, can alleviate a significant amount of individual physician medical malpractice claims.[11] This "enterprise liability" may shift the burden of medical error from physicians to health care organizations.[12] Collective accountability may, therefore, focus on institutional responsibility rather than individual physician negligence.[11,13] Institutions frequently hire multiple specialists and cover their medical malpractice costs as well as stand to be named in suits.

The institutional involvement in malpractice cases also may affect apparent malpractice rates in another way. The National Practitioner Data Bank, which is the source of information for many malpractice studies, only requires reporting about individual physicians, not institutions.[14] If, therefore, claims are settled on behalf of an institution, without implicating the physician, the number of physician malpractice cases may appear to

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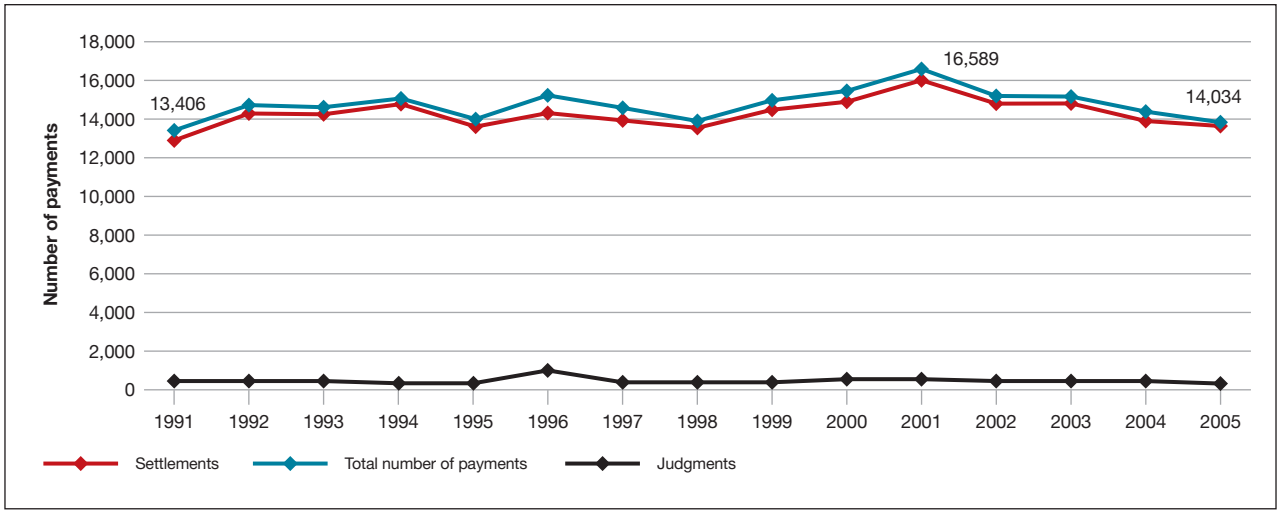
FIGURE 4 Payments for medical malpractice[10]



Total number of malpractice payments with judgments and settlements.

decline without any real change in malpractice rates.[14] In addition, institutions have taken the lead in informal resolution of injuries that occur in the institution, and these programs may reduce the direct malpractice claims against physicians. (These "disclosure, apology, and offer," and similar programs, are discussed in the upcoming third part of this series.)

The medical reform factor

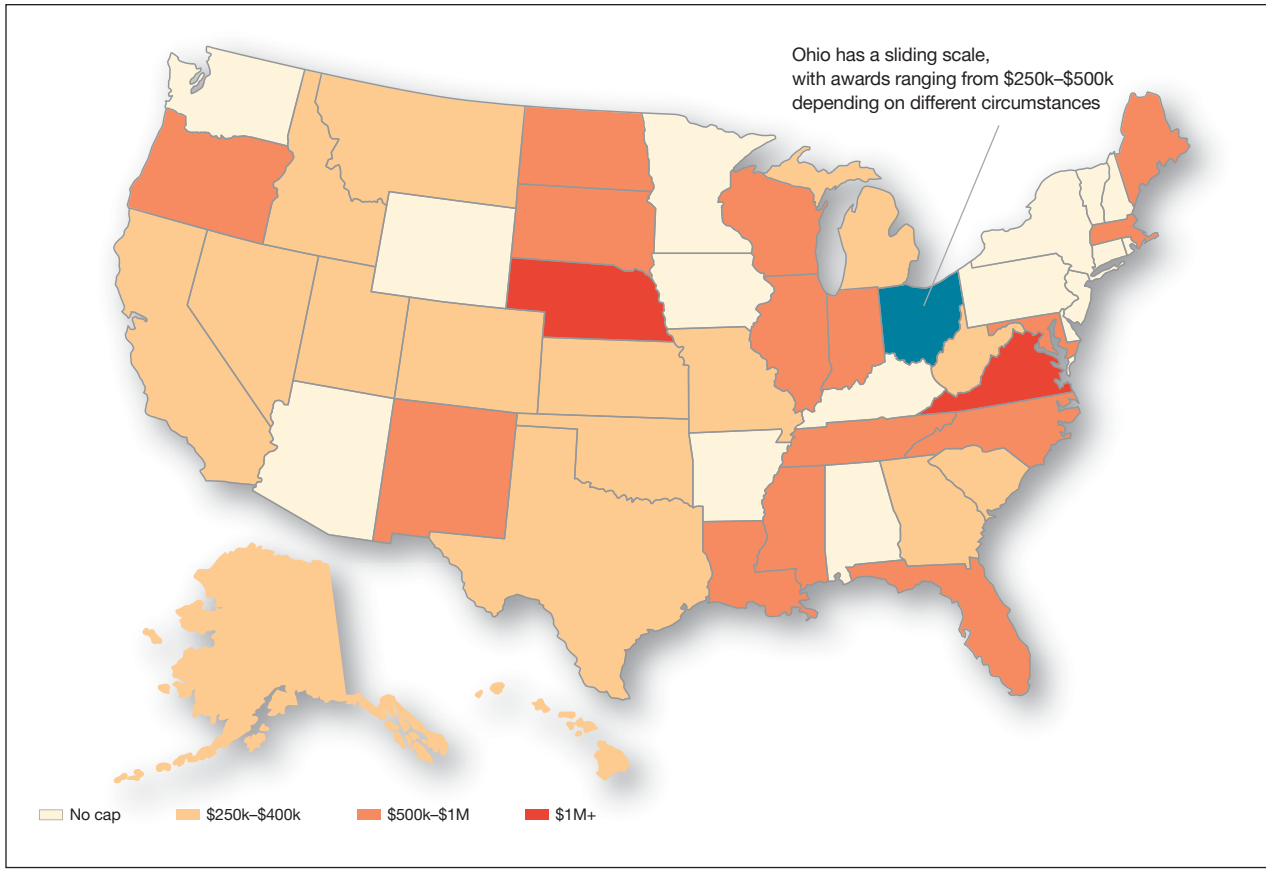
As noted, annual rates paid for medical malpractice in our specialty are trending downward. Many commentators look to malpractice reforms as the reason for the drop in malpractice rates.[15-17] Because medical malpractice is essentially a matter of state law, the medical malpractice reform has occurred primarily at the state level.[18] There have been many different reforms tried—limits on expert witnesses, review panels, and a variety of procedural limitations.[19] Perhaps the most effective reform has been caps being placed on noneconomic damages (generally pain and suffering).[20] These caps vary by state (**FIGURE 5**)[21,22] and, of course, affect the "big verdict" cases. (As we saw in the second case scenario above, Virginia is an example of a state with a cap on malpractice awards.) They also have the secondary effect of reducing the number of malpractice cases. They make malpractice cases less attractive to some attorneys because they reduce the opportunity of large contingency fees from large verdicts. (Virtually all medical malpractice cases in the United States are tried on a contingency-fee basis, meaning that the plaintiff does not pay the attorney handling the case but rather the attorney takes a percentage of any recovery—typically in the neighborhood of 35%.) The reform process continues, although, presently, there is less pressure to act on the malpractice crisis.

Medical malpractice cases are emotional and costly

Another reason for the relatively low rate of paid claims is that medical malpractice cases are difficult, emotionally challenging, time consuming, and expensive to pursue.[23] They typically drag on for years, require extensive and expensive expert consultants as well as witnesses, and face stiff defense (compared with many other torts). The settlement of medical malpractice cases, for example, is less likely than other kinds of personal injury cases.

The contingency-fee basis does mean that injured patients do not have to pay attorney fees up front; however, plaintiffs may have to pay substantial costs along the way. The other

FIGURE 5 An overview of noneconomic medical malpractice caps by state[21,22]



side of this coin is that lawyers can be reluctant to take malpractice cases in which the damages are likely to be small, or where the legal uncertainty reduces the odds of achieving any damages. Thus, many potential malpractice cases are never filed.

A word of caution

The news of a reduction in malpractice paid claims may not be permanent. The numbers can conceivably be cyclical, and political reforms achieved can be changed. In addition, new technology will likely bring new kinds of malpractice claims. That appears to be the case, for example, with electronic health records (EHRs). One insurer reports that EHR malpractice claims have increased over the last 8 years.[24] The most common injury in these claims was death (25%), as well as a magnitude of less serious injuries. EHR-related claims result from system failures, copy-paste inaccuracies, faulty drop-down menu use, and uncorrected "auto-populated" fields. Obstetrics is tied for fifth on the list of 14 specialties with claims related to EHRs, and gynecology is tied for eighth place.[24]

A federal court ruled that a hospital that changed from paper records to EHRs for test results had a duty to "'implement a reasonable procedure during the transition phase' to ensure the timely delivery of test results" to health care providers.[25] We will address this in a future "What's the Verdict?".

Rates of harm, malpractice cases, and the disposition of cases

There are many surprises when looking at medical malpractice claims data generally. The first surprise is how few claims are filed relative to the number of error-related injuries.

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TABLE 2 Goals of tort law

1. Compensation: Provide money to cover the costs of those who were injured by the carelessness of others
2. Deterrence: Reduce injuries (caused by carelessness) by requiring those harming others to pay for the damages they cause. It is appropriate to ask, "How effective and just is this system in the United States?"

Given the estimate of 210,000 to 400,000 deaths "associated with preventable harm" in hospitals, plus 10 to 20 times that number of serious injuries, it would be reasonable to expect claims of many hundreds of thousands per year. Compare the probability of a malpractice claim from an error-related injury, for example, with the probability of other personal injuries—eg, of traffic deaths associated with preventable harm.

The second key observation is how many of the claims filed are not successful—even when there was evidence in the record of errors associated with the injury. Studies slice the data in different ways but collectively suggest that only a small proportion of malpractice claims filed (a claim is generally regarded as some written demand for compensation for injuries) result in payments, either through settlement or by trial. A 2006 study by Studdert and colleagues determined that 63% of formal malpractice claims filed did involve injuries resulting from errors.[26] The study found that in 16% of the claims (not injuries) there was no payment even though there was error. In 10% of the claims there was payment, even in the absence of error.

Overall, in this study, 56% of the claims received some compensation.[26] That is higher than a more recent study by Jena and others, which found only 22% of claims resulted in compensation.[3]

How malpractice claims are decided is also interesting. Jena and colleagues found that only 55% of claims resulted in litigation.[27] Presumably, the other 45% may have resulted in the plaintiff dropping the case, or in some form of settlement. Of the claims that were litigated, 54% were dismissed by the court, and another 35% were settled before a trial verdict. The cases that went to trial (about 10%), overwhelmingly (80%) resulted in verdicts for the defense.[3,27] A different study found that

Why did the 2 opening case vignettes come out differently?

The two vignettes described at the beginning, with similar injuries (shoulder dystocia), had disparate outcomes. In one there was a defense verdict and in the other a verdict for the plaintiffs of more than $2 million. The differences explain a number of important elements related to malpractice claims. (We have only very abbreviated and incomplete descriptions of the cases, so this discussion necessarily assumes facts and jumps to conclusions that may not be entirely consistent with the actual cases.)

These vignettes are unusual in that they went to trial. As we have noted, only a small percentage of malpractice cases are tried. And the verdict for the plaintiff-patient (in the second case) is unusual among those cases that go to trial, where plaintiffs seldom prevail.

From the facts we have, one significant difference in the 2 cases is that the plaintiff's expert witness specifically testified in the second case that the "medical standard of care did not permit traction under these circumstances." That is an essential element of a successful plaintiff's malpractice case. In this case, the expert could also draw a connection between that breach of standard of care and harm to the child. In the case without liability, the nursing staff was able to testify that there was no shoulder dystocia because if there had been such an injury, they would have immediately launched into special action, which did not happen. By contrast, in the liability case, there seemed to be critical gaps in the medical record.

It is also important to remember that these cases were tried in different states, with different laws. The juries and judges in the 2 cases were different. Finally, the quality of the attorneys representing the plaintiffs and defendants were different. We mention these factors to point out that medical malpractice is not an exact science. It depends on many human elements that make the outcome of cases somewhat unpredictable. This unpredictability is one reason why parties and attorneys like to settle cases.

only 9% of cases went to trial, and 87% were a defense verdict.[28] The high level of defense verdicts may suggest that malpractice defense lawyers, and their client physicians, do a good job of assessing cases they are likely to lose, and settling them before trial.

ObGyns generally have larger numbers of claims and among the largest payment amounts when there is payment. Fewer of their cases are dismissed by the courts, so more go to trial. At trial, however, ObGyns prevail at a remarkably high rate.[27] As for the probability of payment of a malpractice claim for ObGyns, one study suggested that there is approximately a 16% annual probability of a claim being filed, but only a 3% annual probability of a payment being made (suggesting about a 20% probability of payment per claim).[3]

The purposes and effects of the medical malpractice system

The essential goals of tort law (including medical malpractice) include compensation for those who are injured and deterrence of future injuries (**TABLE 2**). What are the overall effects to the medical malpractice system? Unfortunately, the answer is that the law delivers disappointing results at best. It has a fairly high error rate. Many people who deserve some compensation for their injuries never seek compensation, and many deserving injured patients fail in efforts to receive compensation. At the same time, a few of the injured receive huge recoveries (even windfalls), and at least a small fraction receive compensation when there was no medical error. In addition to the high error rate, the system is inefficient and very expensive. Both defendants (through their insurance carriers) and plaintiffs spend a lot of money, years of time, and untold emotional pain dealing with these cases. The system also exacts high emotional and personal costs on plaintiffs and defendants.

Malpractice reform has not really addressed these issues—it has generally been focused on ways to reduce the cost of malpractice insurance. The most effective reform in reducing rates—caps—has had the effect of compensating the most seriously injured as though they were more modestly injured, and dissuading attorneys from taking the cases of those less seriously injured.

The medical and legal professions exist to help patients (the public). It does not seem that we have arrived at a system that does that very fairly or efficiently when a patient is injured because of preventable medical error. ●

Watch for the third and final article in this series next month, as we are going to look at "apology in medicine and a proactive response" to communication regarding a complication.

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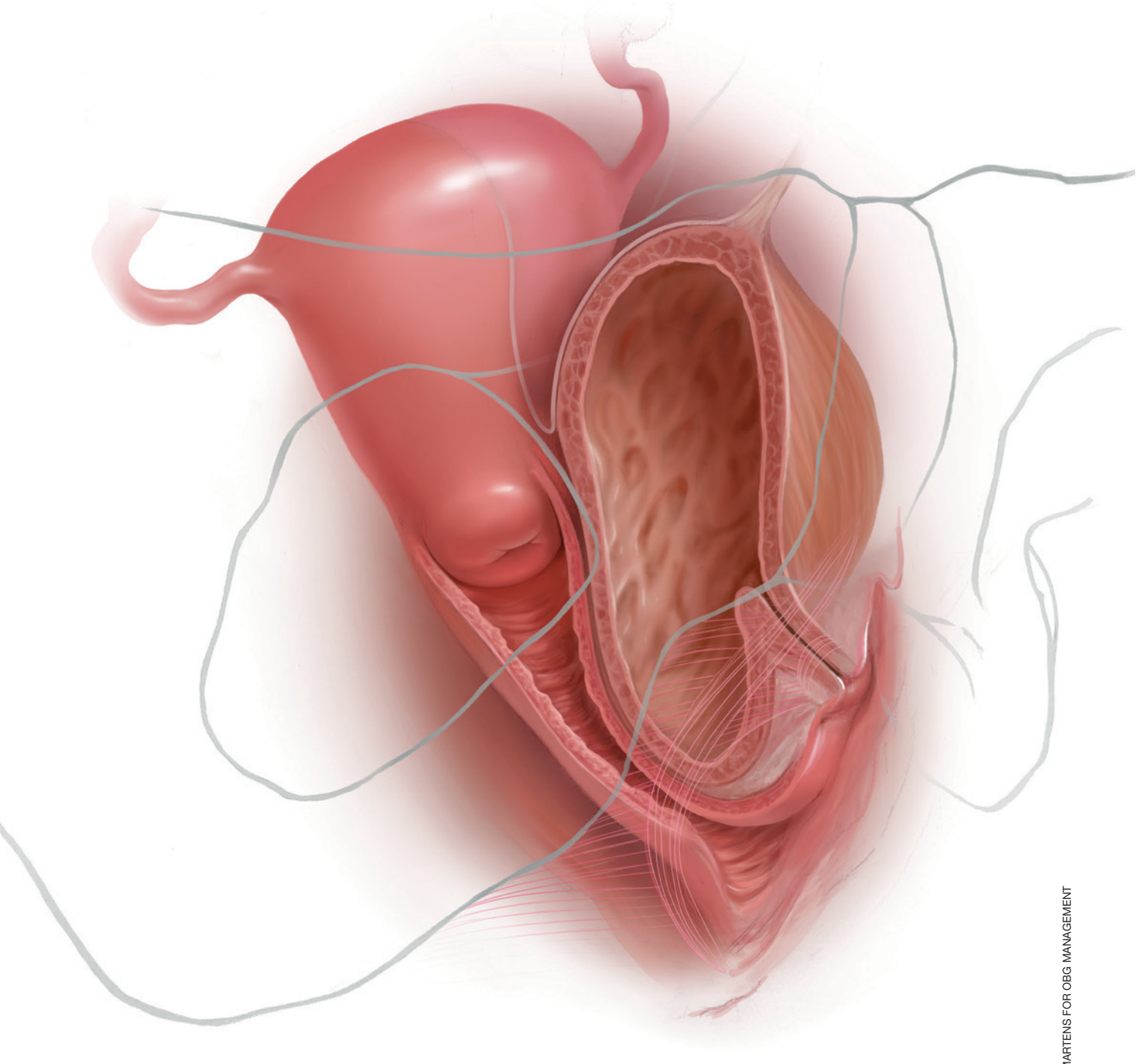

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

ROUNDTABLE

Exploring options for POP treatment: Patient selection, surgical approaches, and ways to manage risks

Four expert gynecologic surgeons offer tips on diagnosis, surgical and nonsurgical treatment approaches, and patient factors to consider

Expert panel featuring John B. Gebhart, MD, MS; Mickey M. Karram, MD; Beri M. Ridgeway, MD; and Mark D. Walters, MD

A number of presentations at the 2019 Pelvic Anatomy and Gynecologic Surgery (PAGS) Symposium (Las Vegas, Nevada, December 12-14, 2019) focused on pelvic organ prolapse (POP) repair, including anatomic considerations, the evolution of surgical procedures, and transvaginal repair. OBG MANAGEMENT caught up with John B. Gebhart, MD, MS, and 3 other experts in gynecologic surgery for a discussion on current approaches for diagnosing and treating POP, including an exchange on the removal of the mesh option for transvaginal prolapse repair.

Nonsurgical approaches for POP: A good option for the right patient

John B. Gebhart, MD, MS: What are the nonsurgical options for POP?

Mark D. Walters, MD: Women who have prolapse could, of course, choose to continue to live with the prolapse. If they desire treatment, however, the main nonsurgical option is a combination of pessary use, possibly with some estrogen, and possibly with pelvic muscle exercises. Women who have a well-fitting pessary can be managed satisfactorily for years. If possible, women should be taught to take the pessary in and out on a regular basis to minimize their long-term complications.

Dr. Gebhart: How can nonsurgical treatment options be maximized?

Beri M. Ridgeway, MD: It depends on patient commitment. This is important to assess at the first visit when you are making management decisions, because if someone is not going to attend physical therapy or not going to continue to do the exercises, the expectation for the outcome is not going to be great.

Also, if a patient feels very uncomfortable using a pessary and really does not want it, I am fine proceeding with surgery as a first-line treatment. If the patient is committed, the ideal is to educate her and connect her with the right people, either a pelvic floor physical therapist or someone in your office who will encourage her and manage pessary use.

Dr. Gebhart: It goes back to assessing patient goals and expectations.

Mickey M. Karram, MD: If you have a patient who is a good candidate for a pessary—say she has a well-supported distal vagina and maybe a cervical prolapse or an apical prolapse—and you can fit a small pessary that will sit in the upper vagina in a comfortable fashion, it is worthwhile to explain to the patient that she is a really good candidate for this option. By contrast, someone who has a wide genital hiatus and a large rectocele will not have good success with a pessary.

Dr. Gebhart: That is important: Choose your

IN THIS ARTICLE

OBG Management Expert Panel

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nonsurgical patients well, those who will respond to therapy and maybe not get frustrated with it.

Dr. Walters: A problem I see is that some people are good at fitting a pessary, but they do not teach how to use it very well. When I see the patient back, she says, "What's my long term on the pessary?" I say, "If we teach you to take it in and out, you are less likely to have any problems with it, and then you can manage it for years that way. Otherwise, you have to keep visiting a practitioner to change it and that is not necessarily a good long-term option." At the very first visit, I teach them what a pessary is, its purpose, and how to maintain it themselves. I think that gives patients the best chance for long-term satisfaction.

Dr. Gebhart: Surgery is always an option if pessary management is not satisfactory.

Dr. Ridgeway: I also tell patients, especially those uncertain about using a pessary, "Worst case, you spend a little time to figure this out, but if it works, you can avoid surgery. If it doesn't—the risks are very low and you perhaps wasted some time—but at least you'll know you tried the conservative management."

Dr. Gebhart: Mickey made an excellent point earlier that it can be a diagnostic treatment strategy as well.

Dr. Karram: If you are concerned about the prolapse worsening or negatively impacting a functional problem related to the bladder or bowel, it is good to place a pessary for a short period of time. This can potentially give you an idea of how your surgery will impact a patient's bladder or bowel function.

Decisions to make before choosing a surgical approach

Dr. Gebhart: Would you elaborate on the surgical options for managing POP?

Dr. Walters: For women with prolapse who decide they want to have surgery, the woman and the surgeon need to make a number of decisions. Some of these include whether the uterus, if present, needs to be removed; whether the woman would like to maintain sexual function or not; whether the repair would best be done vaginally only with native tissue suturing, vaginally with some augmentation (although that is not likely in the United States at this time), or through the abdomen, usually laparoscopically or robotically with a mesh-augmented sacrocolpopexy repair.

Also, we must decide whether to do additional cystocele and rectocele repairs and whether to add slings for stress incontinence, which can coexist or could develop after the prolapse repair. A lot of different decisions need to be made when choosing a prolapse repair for different women.

Dr. Ridgeway: It is shared decision-making with the patient. You need to understand her goals, the degree of prolapse, whether she has contraindications to uterine preservation, and how much risk she is willing to take.

Fundamentals of the clinical evaluation

Dr. Gebhart: For a woman who wants to manage her prolapse surgically, let us consider some fundamentals of clinical diagnosis. Take me through your office evaluation of the patient reporting prolapse symptoms—her history, yes, but from a physical exam standpoint, what is important?

Dr. Karram: You want to know if this is a primary prolapse or recurrent prolapse. You want to distinguish the various segments of the pelvic floor that are prolapsing and try to quantitate that in whatever way you would like. A standardized quantification system is useful, but you should have a system within your practice that you can standardize. Then, determine if there are coexisting functional derangements and how those are being impacted by the prolapse, because that is very important.

Take a good history, and identify how badly the prolapse bothers the patient and affects her quality of life. Understand how much she is willing to do about it. Does she just want to know what it is and has no interest in a surgical intervention, versus something she definitely wants to get corrected? Then do whatever potential testing around the bladder, and bowel, based on any functional derangements and finally determine interest in maintaining sexual function. Once all this information is obtained, a detailed discussion of surgical options can be undertaken.

Dr. Gebhart: What are your clinical pearls for a patient who has prolapse and does not describe any incontinence, voiding dysfunction, or defecatory symptoms? Do we need imaging testing of any sort or is the physical exam adequate for assessing prolapse?

Dr. Walters: When you do the standardized examination of the prolapse, it is important to measure how much prolapse affects the anterior wall of the apex and/or cervix and the posterior wall. Then note that in your notes and plan your surgery accordingly.

It is useful to have the patient fully bear down and then make your measurements; then, especially if she has a full bladder, have her cough while you hold up the prolapse with a speculum or your hand to see if she has stress urinary incontinence.

Dr. Ridgeway: I agree that to diagnose prolapse, it is physical exam alone. I would not recommend any significant testing other than testing for the potential for stress incontinence.

Dr. Gebhart: Is it necessary to use the POP-Q (Pelvic Organ Prolapse Quantification system) in a nonacademic private practice setting? Or are other systems, like a Baden-Walker scoring system, adequate in the everyday practice of the experienced generalist?

Dr. Walters: The Baden-Walker system actually is adequate for use in everyday practice. However, Baden-Walker is an outdated measurement system that really is not taught anymore. I think that as older physicians finish and newer doctors come in, no one will even know what Baden-Walker is.

It is better to go ahead and start learning the POP-Q system. Everyone has electronic charts now and if you learn to use the POP-Q, you can do it very quickly and get a grading system for your chart that is reproducible for everyone.

Dr. Ridgeway: The most important thing is to assess all 3 compartments and document the amount of prolapse of each compartment. A modified POP-Q is often adequate. To do this, perform a split speculum exam and use the hymen as the reference. Zero is at the hymen, +1 is 1 cm beyond the hyman. Covering the rectum, how much does the anterior compartment prolapse in reference to the hymen? Covering the anterior compartment, get an idea of what is happening posteriorly. And the crux of any decision in my mind is what is happening at the apex or to the uterus/cervix if it is still present. It is really important to document at least those 3 compartments.

Dr. Karram: I agree. The POP-Q is the ideal, but I don't think generalists are motivated to use it. It is very important, though, to have some anatomic landmarks, as already mentioned by Dr. Ridgeway.

Choose a surgical approach based on the clinical situation

Dr. Gebhart: How do you choose the surgical approach for someone with prolapse?

> "The most important thing is to assess all 3 compartments and document the amount of prolapse in each compartment."
>
> —*Beri M. Ridgeway, MD*

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Dr. Karram: Most surgeons do what they think they do best. I have spent the majority of my career operating through the vagina, and most of that involves native tissue repairs. I almost always will do a primary prolapse through the vagina and not consider augmentation except in rare circumstances. A recurrent prolapse, a prolapsed shortened vagina, scarring, or a situation that is not straightforward has to be individualized. My basic intervention initially is almost always vaginally with native tissue.

Dr. Ridgeway: For a primary prolapse repair, I also will almost always use native tissue repair as firstline. Whether that is with hysterectomy or without, most people in the long term do very well with that. At least 70% of my repairs are done with a native tissue approach.

For a woman who has a significant prolapse posthysterectomy, especially of the anterior wall or with recurrent prolapse, I offer a laparoscopic sacrocolpopexy. The only other time I offer that as a primary approach would be for a younger woman with very significant prolapse. In that case, I will review risks and benefits with the patient and, using shared decision-making, offer either a native tissue repair or a sacrocolpopexy. For that patient, no matter what you do, given that she has many years to live, the chances are that she will likely need a second intervention.

Dr. Gebhart: Mark, how do you choose an approach for prolapse?

Dr. Walters: I do things pretty much the way Dr. Karram and Dr. Ridgeway do. For women who have a primary prolapse, I usually take a vaginal approach, and for recurrences I frequently do sacrocolpopexy with mesh or I refer to one of my partners who does more laparoscopic or robotic sacrocolpopexy.

Whether the patient needs a hysterectomy or not is evolving. Traditionally, hysterectomy is almost always done at the first prolapse repair. That is being reassessed in the United States to match what is happening in some other countries. It is possible to do nice primary prolapse repair vaginally or laparoscopically and leave the uterus in, in selected women who desire that.

> "For women who have primary prolapse, I usually take a vaginal approach, and for recurrences I frequently do sacrocolpopexy with mesh or I refer to one of my partners who does more laparoscopic or robotic sacrocolpopexy."
>
> *—Mark D. Walters, MD*

Transvaginal prolapse repair: Mesh is no longer an option

Dr. Gebhart: What led up to the US Food and Drug Administration's (FDA) market removal of mesh for transvaginal repair of POP?

Dr. Ridgeway: To clarify, it was not a recall—a word that many people use—it was an order to stop producing and distributing surgical mesh intended for transvaginal repair of POP.[1] There is a very long history. Transvaginal mesh was introduced with the goal of improving prolapse anatomic and subjective outcomes. Over the last 13 years or so, there were adverse events that led to FDA public health notifications. Consequently, these devices were reclassified, and now require additional testing prior to approval. The newest transvaginal mesh kits were studied.

These 522 studies were completed recently and needed to show superior outcomes because, historically, the risks associated with transvaginal mesh compared to those associated with native tissue repairs are higher: higher reoperation rates, higher rates of other complications, and very minimal improvements in subjective and objective outcomes. Data were presented to the FDA, and it was deemed that these mesh kits did not improve outcomes significantly compared with native tissue repairs.

Dr. Karram: Beri, you stated that very accurately. The pro-mesh advocates were taken back by the idea that the FDA made this recommendation without allowing the outcomes to be followed longer.

Dr. Gebhart: My understanding is that the FDA had a timeline where they had to do a report and the studies had not matured to that end point; thus, they had to go with the data they had even though the studies were not completed. I think they are requesting that they be completed.

Dr. Ridgeway: Additional data will be available, some through the 522 studies, others through randomized controlled trials in which patients were already enrolled and had surgery. As far as I know, I do not think that the decision will be reversed.

Native tissue repair and failure risk

Dr. Gebhart: I hear a lot that native tissue repairs fail. Mickey, as you do a lot of vaginal surgery, what are your thoughts? Should you use augmentation of some sort because native tissue fails?

Dr. Karram: There is going to be a failure rate with whatever surgery you do. I think that the failure rate with native tissue is somewhat overstated. I think a lot of that dates back to some of the things that were being promoted by mesh advocates. Initially, there was a lot of cherry-picking of native tissue data in some of those studies to promote the idea that the recurrent prolapse rates were 40% to 80%. We certainly do not see that in our patient population.

Based on our 5-year data, we have a recurrence rate of about 15% and a reoperation rate of less than 10%. That is the best I can quote based on our data. We have not followed patients longer than 5 years.

I can't do much better than that with an augmentation; even if I get another 5% or 10% better anatomic outcome, that will be at the expense of some erosions and other complications specific to the mesh. I do think that the native tissue failure rate being promoted by a lot of individuals is a higher failure rate than what we are seeing.

Dr. Gebhart: What do you think, Mark?

Dr. Walters: Large cohort studies both at your institution, Mayo Clinic, and ours at the Cleveland Clinic mirror what Dr. Karram said, in that we have a reoperation rate somewhere between 8% and 15%. Of course, we have some failures that are stage 2 failures where patients choose not to have another operation. In general, a 10% or 12% reoperation rate at 5 to 7 years is acceptable.

Native tissue repairs probably fail at the apex a little more than mesh sacrocolpopexy. Mesh sacrocolpopexy, depending on what else you do with that operation, may have more distal vaginal failures, rates like distal rectoceles and more de novo stress urinary incontinence than we probably get with native tissue. I get some failures of the apex with native tissue repairs, but I am okay with using sacrocolpopexy as the second-line therapy in those patients.

Hysteropexy technique and pros and cons

Dr. Gebhart: Is hysteropexy a fad, or is there something to this?

Dr. Ridgeway: I do not think it is a fad. Women do feel strongly about this, and we now have data supporting this choice: randomized controlled trials of hysterectomy and prolapse repair versus hysteropexy with comparable outcomes at the short and medium term.[2]

The outcomes are similar, but as we said, outcomes for all prolapse repair types are not perfect. We have recurrences with sacrocolpopexy, native tissue repair, and hysteropexy. We need more data on types of hysteropexy and long-term outcomes for uterine preservation.

Dr. Walters: We have been discussing what patients think of their uterus, and some patients have very strong opinions. Some prefer to have a hysterectomy because then they don't need to worry about cancer or do screening for cancer, and they are very happy with that. Other women with the same kind of prolapse prefer not to have a hysterectomy because philosophically they think they are better off keeping their organs. Since satisfaction is an outcome, it is useful to know what the patient wants and what she thinks about the surgical procedure.

Dr. Gebhart: For hysteropexy, do the data show that suture or a mesh augment provide an advantage one way or the other? Do we know that yet?

Dr. Walters: No, there are not enough studies with suture. There are only a few very good studies with suture hysteropexy, and they are mostly sacrospinous suture hysteropexies. Only a few studies look at mesh hysteropexy (with the Uphold device that was put on hold), or with variations of uterosacral support using strips of mesh, mostly done in other countries.

A point I want to add, if native tissue repairs fail at the apex more, why don't you just always do sacrocolpopexy? One reason is because it might have a little higher complication rate due to the abdominal access and the fact that you are putting mesh in. If you have, for example, a 4% complication rate with the

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>
> *—Mickey M. Karram, MD*

mesh but you get a better cure rate, those things balance out, and the woman may not be that much better off because of the extra complications. You have to assess the pro and con with each patient to pick what is best for her—either a more durable repair with a mesh or a little safer repair with native tissue.

Dr. Ridgeway: Women feel very strongly about risk. Within the same clinic I will have similar patients, and I say, "Probably in the long term this one may last a little longer but the surgery takes longer and it has a little higher complication rate." One patient will say, "I'm not worried about the risk, I want what's going to last the longest," whereas a very similar patient will say, "Why would anyone pick the higher-risk operation? I want the lower risk that probably will last a long time."

Dr. Gebhart: Beri, who should not have a hysteropexy?

Dr. Ridgeway: The biggest factor would be someone who has ever had postmenopausal bleeding. From our data, we know that if they have even had a work-up with benign results, the risk of unanticipated pathology is high. I do not recommend hysteropexy for anyone who has had postmenopausal bleeding.

For a premenopausal woman who has irregular bleeding, I also do not recommend it, because you just do not know what that future will hold. If a patient has anatomic abnormalities like large fibroids, I would not recommend it either. I would like patients to have had standard cervical cancer screening without any abnormalities for about 10 years or so.

Dr. Gebhart: What about prior cervical dysplasia?

Dr. Ridgeway: If a patient had ASCUS or low-grade dysplasia decades ago, has been normal for at least 10 years, and is currently negative for human papillomavirus, I have no problem.

Dr. Gebhart: How about women at high genetic risk for cancer?

Dr. Ridgeway: If they are at high risk for endometrial cancer, I would not recommend hysteropexy. If they are going to need an oophorectomy and/or salpingectomy for risk reduction during prolapse treatment, I usually perform a hysterectomy.

> "I do not recommend hysteropexy for anyone who has had postmenopausal bleeding. For a premenopausal woman who has irregular bleeding, I also do not recommend it, because you just do not know what the future will hold."
>
> —*Beri M. Ridgeway, MD*

Plan surgical steps and prepare for "what if's"

Dr. Gebhart: What tips can you provide, either regarding the evaluation or something you do surgically, that are important in a transvaginal native tissue repair?

Dr. Karram: If you have a case of posthysterectomy apical prolapse, that you think is an indication for sacrocolpopexy, in reality these are very good candidates for either sacrospinous or uterosacral suspensions. I prefer a uterosacral suspension as I feel there is less distortion of the vaginal apex compared to a sacrospinous suspension.

Dr. Ridgeway: The most critical step is setting up the OR and positioning the patient. That sets up the case for success, preventing struggles during the case. I use a high lithotomy, with careful positioning of course, but I use candy cane stirrups so that I can have an instrument stand in front of me and not struggle during the case.

Dr. Walters: My tip for everyone who is doing native tissue surgery, whether it is high McCall colpopexy or uterosacral ligament suspension or sacrocolpopexy, would be to really learn well the anatomy of each operation, including how close the ureter is, where the risk for bleeding is, and where the risk for nerve damage is.

The complications for each of these surgeries are slightly different, but there is a small risk of kinking the ureter with both uterosacral ligament suspension and the McCall, so you should do a cystoscopy as part of that operation. If you do a sacrospinous ligament suspension, use an instrument that can get a stitch into a ligament—not too close to the ischial spine and not too close to the sacrum—to avoid the risk of damage to major nerves and blood vessels and to minimize buttock and leg pain.

Dr. Karram: Another tip is to understand that you are going to have potential complications intraoperatively. Think through those presurgically. You do not want to start thinking about these things and making decisions as they are happening. For example, what if I do a uterosacral suspension and I don't see efflux of urine from the ureter? What am I going to

do, and how long am I going to wait before I intervene? If I do a sacrospinous and I start to see a lot of bleeding from that area, what am I going to do? My plan would be, "I will pack the area, get extra suction, etc." Thinking these ideas through before they occur is very helpful.

Dr. Gebhart: That is critical, to have an algorithm or a scheme in your mind. You want to think through it before it occurs because you are not always thinking as clearly when things are not going well.

I would say get good at physical examination skills in the office, then have a plan for the OR based on what you see in the office. If what is going on with the prolapse is not completely investigated and other issues are not addressed, then failure results because you did not make the diagnosis. Certainly, modify the procedure according to what you find intraoperatively, but follow through.

Indications and tips for sacrocolpopexy

Dr. Gebhart: What are the indications for sacrocolpopexy?

Dr. Ridgeway: Indications include recurrent apical prolapse, posthysterectomy prolapse, or severe prolapse in someone quite young. It is a fantastic operation with overall low risks, but this needs to be discussed with the patient.

Dr. Walters: There are some unusual circumstances—for example, the woman has a short prolapsed vagina, usually after a prior surgery—in which the best repair is a bridging piece of mesh, usually done laparoscopically, because those operations cannot be done very well vaginally to obtain a durable result.

Dr. Karram: I agree. I do not think that all recurrent prolapses mandate a sacrocolpopexy. You need to individualize, but in general the short prolapsed vagina and patients who are very young are at high risk for a recurrence.

Dr. Gebhart: An older patient might be a very good candidate, even if she had recurrence from another vaginal repair.

Beri, does the patient with a high body mass index need augmentation?

Dr. Ridgeway: That is a great question, and this has to be individualized because, while heavier patients can benefit from augmentation, in a very heavy patient, getting into that abdomen has its own set of challenges. Anatomically they get a better repair with a mesh-augmented repair like a sacrocolpopexy, but they do have increased risks. That is important to acknowledge and clarify with the patient.

Dr. Gebhart: Any surgical tip you might offer on sacrocolpopexy?

Dr. Ridgeway: Perform the operation in the same way you would an open procedure. Meaning, use the same materials, the same sutures, the same placement, and the same type of dissection in order to obtain results similar to those with an open operation. Using your assistants to manipulate the vagina and rectum is important, as well as exposure and typical careful surgical technique.

Dr. Gebhart: What is important about the placement of sutures on the anterior longitudinal ligament, and what do you need to be cognizant of?

Dr. Ridgeway: Be careful of that left common iliac vein that is a little more medial than you would expect and of the middle sacral artery, and try to differentiate between L5 and S1. In an ideal circumstance, place the suture at S1 or L5 but not the inner disc space, which is the area to avoid placement.

Historically, the recommendation is S1. Some people do L5 because of some pull out strength studies, but also because it is easier, and sometimes in that area of the anterior longitudinal ligament is much better. The key is to do enough dissection and use haptic feedback, especially with conventional laparoscopy or an open approach, to avoid placing sutures through the disc space, as there is some concern that it increases the risk for discitis or osteomyelitis in that area.

Dr. Gebhart: We also have found that if you have a combined surgery with colorectal colleagues, like a rectal prolapse repair, there is a little higher risk of discitis.

Dr. Ridgeway: In my own practice I saw a combined case with a rectopexy in

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>
> —*John B. Gebhart, MD, MS*

someone who had a biologic mesh erosion. When we reviewed the literature, a number of reported cases of discitis had either an early post-op or concurrent urinary tract infection or vaginal infection that likely predisposed them to an infection that traveled up the material.

Dr. Karram: My final comment is that a sacrocolpopexy is not a few stitches or a little mesh right at the apex. If the patient has an isolated enterocele, okay, but it is a wide mesh for a reason and it should connect to the endopelvic fascia anteriorly, posteriorly. It is a mistake to suture just a little bit of the cuff and grab it and think, "I've done a colpopexy" when the procedure has not been executed as it should be.

Dr. Gebhart: I want to thank our expert panel and OBG MANAGEMENT for providing this discussion opportunity. Thank you. ●

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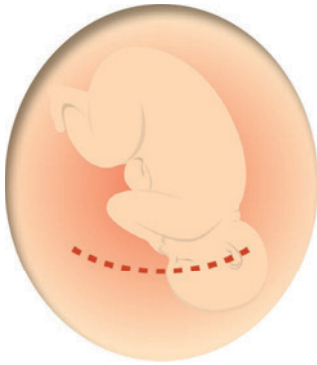


ERAS for cesarean delivery: Intraoperative care

Enhanced recovery after surgery (ERAS) has been shown to improve patient outcomes and save resources. Using ERAS Society principles, the following elements have been recommended under author consensus for "process-directed maternal care" for intraoperative cesarean delivery (CD). (Watch for recommended postoperative elements in a future issue.)

Intraoperative pathway

Administer IV antibiotics within 60 minutes before the CD incision

For abdominal skin cleansing, use clorhexidine-alcohol versus aqueous povidone-iodine solution

Consider preparing the vagina with povidone-iodine solution to reduce post-CD infection

Use regional anesthesia as the preferred method of anesthesia for CD

Avoid hypothermia with appropriate patient monitoring and warming devices during CD (recommended for hypothermia prevention: forced air warming, IV fluid warming, increased OR temperature)

Maintain perioperative and intraoperative euvolemia to improve maternal and neonatal outcomes

Surgical technique considerations

Use blunt expansion of a transverse uterine hysterotomy to reduce surgical blood loss

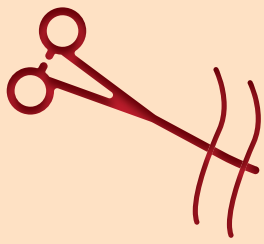
Close the hysterotomy in 2 layers to lower the rate of uterine rupture

Do not close the peritoneum to decrease operative time with no effect on outcomes

Reapproximate the tissue layer in women with ≥2 cm of subcutaneous tissue

Use subcuticular suture for skin closure in most cases

Neonate pathway



Term delivery: Delay cord clamping for ≥1 min

Preterm delivery: Delay cord clamping for ≥30 sec

Maintain body temperature between 36.5° and 37.5° Celsius

Avoid routine airway suction or gastric aspiration (use only for obstructive airway symptoms)

Provide neonatal supplementation with room air versus inspired air with oxygen

Have capacity for immediate neonatal resuscitation in all settings that perform CD

[a]First-generation cephalosporin is recommended in all women; in women in labor or with ruptured membranes, adding azithromycin further reduces postoperative infections.

Source: Caughey AB, Wood SL, Macones GA, et al. Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society recommendations (part 2). *Am J Obstet Gynecol*. 2018;219:533-544.

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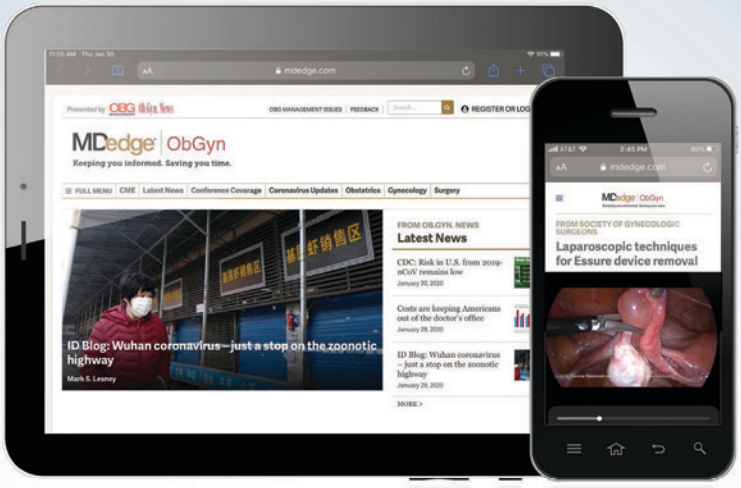

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Sex last night?

A negative fFN result *is* valid.

Even if a patient has had sex in the prior 24 hours:

- A negative result ***is*** valid
- A positive result may not be valid & should be confirmed > 24 hours[1]

The majority of patients will test negative, even if they've had sex in the prior 24 hours.[2]

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Reference: 1. Rapid fFN for the Tli$_{IQ}$ System [package insert]. AW-04196, Sunnyvale, CA: Hologic, Inc.; 2017. **2.** McLaren JS, et al. Prediction of spontaneous preterm birth using quantitative fetal fibronectin after recent sexual intercourse. *Am J Obstet Gynecol.* 2015; 212:89e1-5.