MDEDGE.COM/OBGYN | VOL 32, NO 10 | OCTOBER 2020

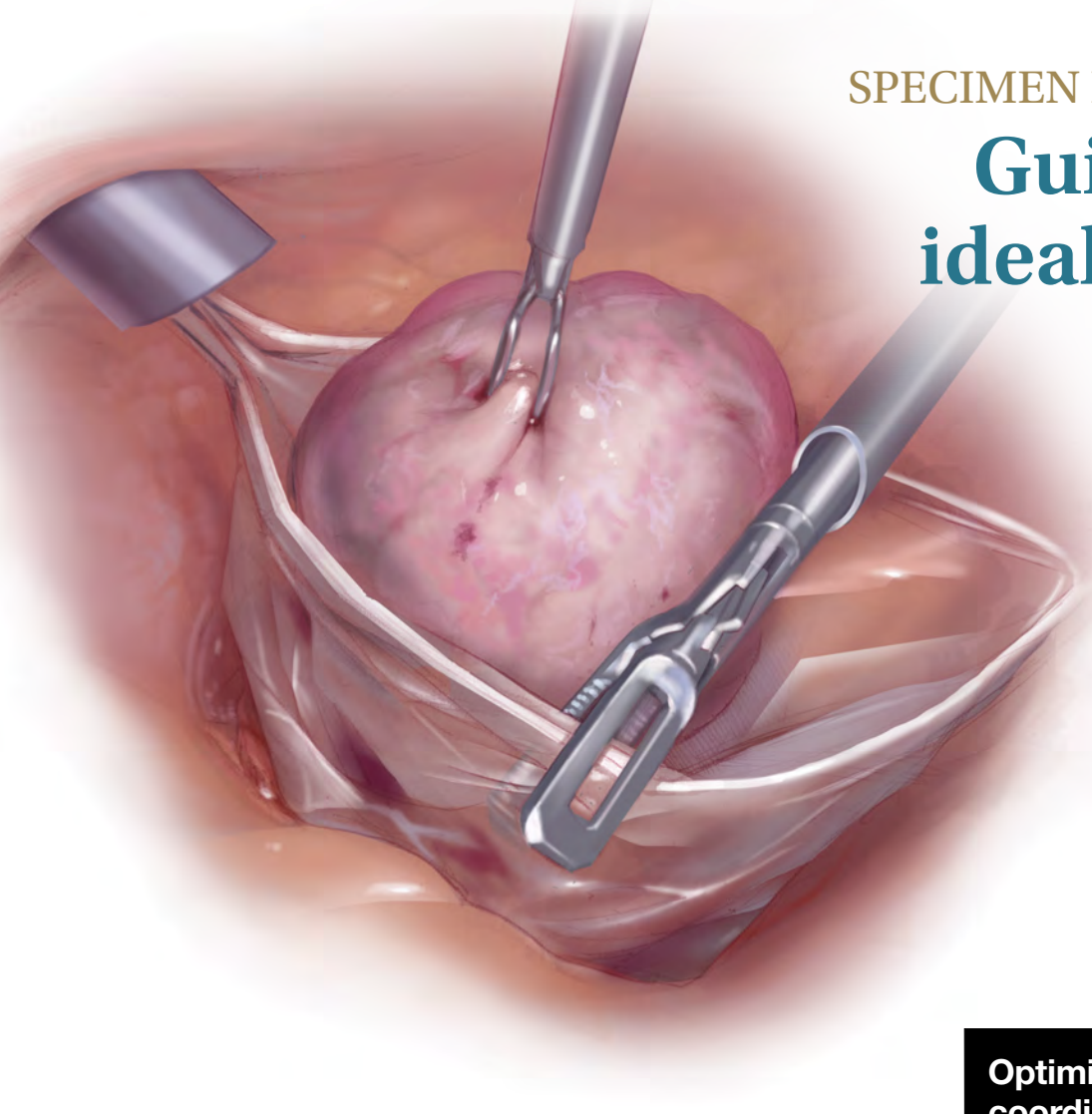
OBG MANAGEMENT

A member of the MDedge Network

Society of Gynecologic Surgeons Annual Meeting Highlights Issue

"Elective" should not be a descriptor for important ObGyn procedures
Robert L. Barbieri, MD

Update on contraception



SPECIMEN RETRIEVAL BAGS

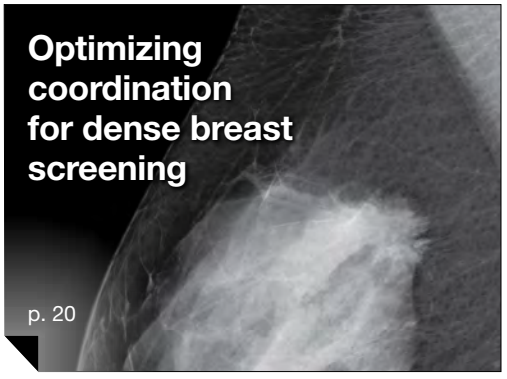
Guidance for ideal selection

Tiffany Sia, MD;
Hye-Chun Hur, MD, MPH

Work-life balance in gyn surgery

Urethral bulking agents for SUI

Should we abandon breast cancer screening for average-risk women in their 40s?
only at mdedge.com/obgyn



Improve Recovery After C-Section With Long-Lasting, Non-Opioid Pain Control

Multimodal pain management with **EXPAREL** provided significantly better pain control after C-section vs multimodal protocols alone[1,2] and...

52% **REDUCED postsurgical opioid use*** (MED) over 72 hours vs standard bupivacaine TAP block (*P*=0.0117)[2†]

12 hours **REDUCED time to ambulation** vs multimodal protocol without EXPAREL (*P*<0.001)[1‡]

1 day **REDUCED hospital LOS** by 1 day (*P*<0.001); 2.9 days (n=97) vs 3.9 days (n=89)[1‡]

Improve clinical and economic outcomes. **Learn more at www.EXPAREL.com/OBGyn**

LOS, length of stay; MED, morphine equivalent dose; TAP, transversus abdominis plane.
*The clinical benefit of the decrease in opioid consumption was not demonstrated in the pivotal trials.
†A prospective, 13-site, multicenter, randomized clinical trial of 186 patients who underwent a C-section with a multimodal pain management protocol, including a TAP block using either 20 mL EXPAREL 266 mg, 20 mL 0.25% bupivacaine HCl, and 20 mL normal saline (30 mL volume on each side) for a total volume of 60 mL; or 20 mL 0.25% bupivacaine HCl and 40 mL normal saline (30 mL volume on each side) for a total volume of 60 mL.[2,3]
‡Single-center retrospective trial of 201 patients who underwent C-section with either a multimodal pain management protocol induding a TAP block with 20 mL EXPAREL 266 mg, 30 mL 0.25% bupivacaine HCl, and 30 mL normal saline; or a multimodal pain management protocol alone. Mean hospital LOS was 2.9 days with EXPAREL (n=97) vs 3.9 days without EXPAREL (n=89). Time to ambulation was 18.7 hours with EXPAREL (n=67) and 30.7 hours without EXPAREL (n=60).[1]

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

Important Safety Information
EXPAREL is contraindicated in obstetrical paracervical block anesthesia. Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation. If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine. EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.
Warnings and Precautions Specific to EXPAREL: Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL. EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks **other than interscalene brachial plexus nerve block**, or intravascular or intra-articular use. The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.
Warnings and Precautions for Bupivacaine-Containing Products
Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression. **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death. **Allergic Reactions:** Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use. **Methemoglobinemia:** Cases of methemoglobinemia have been reported with local anesthetic use.

Please refer to brief summary of full Prescribing Information on adjacent page.
Full Prescribing Information is available at www.EXPAREL.com.
For more information, please visit www.EXPAREL.com or call 1-855-RX-EXPAREL (793-9727).

References: 1. Baker BW, Villadiego LG, Lake YN, et al. Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. *J Pain Res.* 2018;11:3109-3116. **2.** Habib AS, Nedeljkovic SS, Kett A, et al. Liposomal bupivacaine transversus abdominis plane block for pain after cesarean delivery: results from a multicenter, randomized, double-blind, controlled trial. Presented at: SOAP 51st Annual Meeting; May 4, 2019; Phoenix, AZ. **3.** ClinicalTrials.gov website. Evaluate the safety and efficacy of EXPAREL when administered via infiltration into the TAP vs bupivacaine alone in subjects undergoing elective c-sections (c-section). https://clinicaltrials.gov/ct2/show/NCT03176459. Updated April 22, 2019. Accessed May 31, 2019. This study was supported by a grant from Pacira BioSciences, Inc.

PACIRA BIOSCIENCES, INC.

Parsippany, NJ 07054 PP-EX-US-5727 04/20

NON-OPIOID
EXPAREL®
(bupivacaine liposome injectable suspension)

EXPAREL®

(bupivacaine liposome injectable suspension)

Brief Summary
(For full prescribing information refer to package insert)

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Warnings and Precautions Specific for EXPAREL

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

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

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

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

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

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

- patients younger than 18 years old
- pregnant patients

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

ADVERSE REACTIONS

Clinical Trial Experience

Adverse Reactions Reported in Local Infiltration Clinical Studies

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

Adverse Reactions Reported in Nerve Block Clinical Studies

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

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

Postmarketing Experience

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

DRUG INTERACTIONS

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

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

Examples of Drugs Associated with Methemoglobinemia:

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

Bupivacaine

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

Non-bupivacaine Local Anesthetics

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

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

Water and Hypotonic Agents

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

Labor or Delivery

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

Clinical Presentation

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

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

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

Management of Local Anesthetic Overdose

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

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

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

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

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Information

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

Recommended Dosing in Adults

Local Analgesia via Infiltration

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

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

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

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

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

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

Compatibility Considerations

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

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

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

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

Non-Interchangeability with Other Formulations of Bupivacaine

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

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

PATIENT COUNSELING

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

PACIRA PHARMACEUTICALS, INC.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

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

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

Rx only **November 2018**

#1 IN READERSHIP*

OBG MANAGEMENT

mdedge.com/obgyn

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

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

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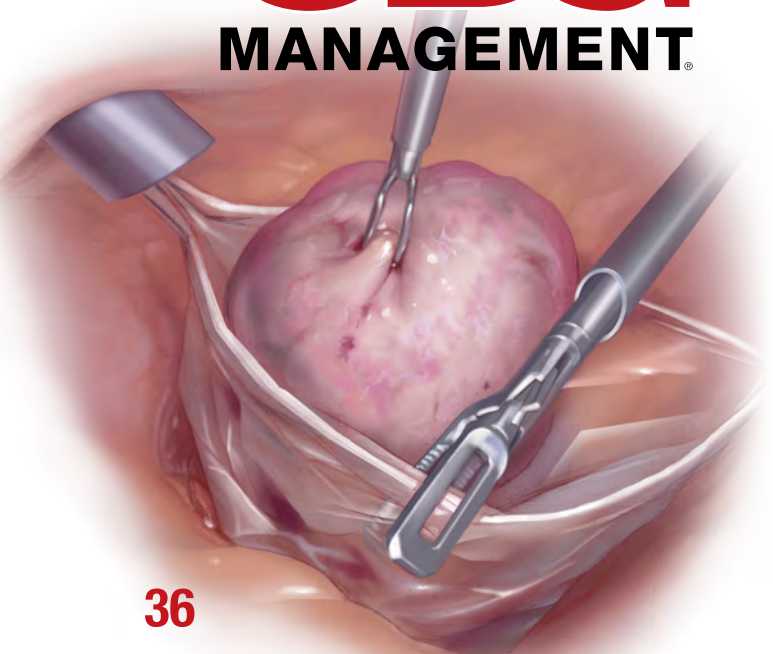
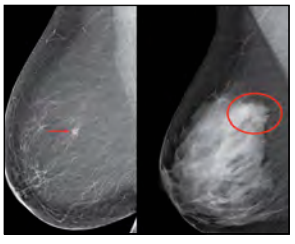
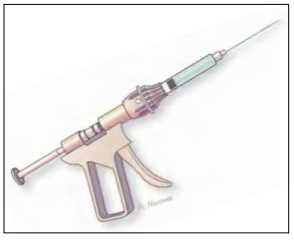




Dense breasts 20



Urethral bulking 25

FAST TRACK **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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COVER IMAGE: KIMBERLY MARTENS

ANNOVERA® IS ANNUAL BIRTH CONTROL OWNED AND OPERATED BY HER[1]*

Meet the innovative contraception designed to empower women

Created for her control: Long-lasting, reversible, and procedure-free[1]

Created for her comfort: Soft and flexible for easy insertion and removal[1,2]

Created with a novel hormone profile: Purposefully designed to release a combination of a non-androgenic progestin and a low-dose estrogen daily for 1 year (13 cycles)[1,3]

*ANNOVERA is inserted for 21 continuous days and removed for 7 days for 13 cycles.

ANNUAL.
COMFORTABLE.
CONTROLLABLE.

Annovera®
(segesterone acetate and ethinyl estradiol vaginal system)
Delivers 0.15 mg/0.013 mg per day

Give her birth control that she controls.

AnnoveraHCP.com

IMPORTANT SAFETY INFORMATION

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

INDICATION

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

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

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

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

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ANVA-20142.2 09/2020

ANNOVERA® (segesterone acetate and ethinyl estradiol vaginal system)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders and Other Vascular Conditions

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

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

Arterial Events

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

Venous Events

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

Liver Disease

Impaired Liver Function

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

Liver Tumors

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

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

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

Hypertension

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

Age-Related Considerations

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

Gallbladder Disease

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

Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

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

Dyslipidemia

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

Headache

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

Bleeding Irregularities and Amenorrhea

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

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

Depression

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

Cervical Cancer

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

Effect on Binding Globulins

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

Hereditary Angioedema

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

Chloasma

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

Toxic Shock Syndrome (TSS)

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

Vaginal Use

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

ADVERSE REACTIONS

Clinical Trial Experience

Most Common Adverse Reactions

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

Adverse Reactions Leading to Discontinuation

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

Serious Adverse Reactions

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Discontinue ANNOVERA if pregnancy occurs.

Lactation

Not recommended for nursing mothers; can decrease milk production.

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

Renal Impairment

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

Body Mass Index (BMI)/Body Weight

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

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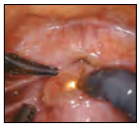

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EDITORIAL

Please stop using the adjective "elective" to describe the important health services ObGyns provide

Calling a health intervention "elective" risks miscommunicating that it is unnecessary or should have a lower priority than "indicated" interventions. We can avoid this confusion if we discontinue the use of "elective" to describe ObGyn procedures.

Robert L. Barbieri, MD
Editor in Chief

During the April 2020 peak of patient admissions to our hospital caused by coronavirus disease 2019 (COVID-19), we severely limited the number of surgical procedures performed to conserve health system resources. During this stressful time, some administrators and physicians began categorizing operations for cancer as "elective" procedures that could be postponed for months. Personally, I think the use of elective to describe cancer surgery is not optimal, even during a pandemic. In reality, the surgeries for patients with cancer were being postponed to ensure that services were available for patients with severe and critical COVID-19 disease, not because the surgeries were "elective." The health system leaders were making the rational decision to prioritize the needs of patients with COVID-19 infections over the needs of patients with cancer. However, they were using an inappropriate description of the rationale for postponing the surgery for patients with cancer—an intellectual short-cut.

This experience prompted me to explore all the medical interventions commonly described as elective. Surprisingly, among medical specialists, obstetricians excel in using the adjective elective to describe our important work. For example, in the medical record we commonly use terms such as "elective induction of labor," "elective cesarean delivery" (CD) and "elective termination of pregnancy." I believe it would advance our field if obstetricians stopped using the term elective to describe the important health services we provide.

doi: 10.12788/obgm.0041

Stop using the term "elective induction of labor"

Ghartey and Macones recently advocated for all obstetricians to stop using the term elective when describing induction of labor.[1] The ARRIVE trial (A Randomized Trial of Induction vs Expectant Management)[2] demonstrated that, among nulliparous women at 39 weeks' gestation, induction of labor resulted in a lower CD rate than expectant management (18.6% vs 22.2%, respectively; relative risk, 0.84; 95% confidence interval [CI], 0.76-0.93). These findings indicate that induction of labor is not elective because it provides a clear health benefit over the alternative of expectant management. Given current expert guidance, induction of labor prior to 39 weeks' gestation must be based on an accepted medical indication and provide a health benefit; hence, these inductions are medically indicated. Similarly, since induction of labor at 39 weeks' gestation also provides a clear health benefit it is also medically indicated and not "elective." Ghartey and Macones conclude[1]:

> The words we choose to describe medical interventions matter. They send a message to patients, physicians, nurses, and hospital administrators. When the term "elective" is applied to a medical intervention, it implies that it is not really necessary. That is certainly not the case when it comes to 39-week nulliparous induction. The ARRIVE trial provides grade A (good and consistent) evidence that labor induction provided benefit with no harm to women and their infants. These inductions are not "elective."

An alternative descriptor is "medically indicated" induction.

Stop using the term "elective cesarean delivery"

I recently searched PubMed for publications using the key words, "elective cesarean delivery," and more than 7,000 publications were identified by the National Library of Medicine. "Elective cesarean delivery" is clearly an important term used by obstetrical authorities. What do we mean by elective CD?

At 39 weeks' gestation, a low-risk nulliparous pregnant woman has a limited number of options:

1. induction of labor
2. expectant management awaiting the onset of labor
3. scheduled CD before the onset of labor.

For a low-risk pregnant woman at 39 weeks' gestation, the American College of Obstetricians and Gynecologists recommends vaginal delivery because it best balances the risks and benefits for the woman and newborn.[3] When a low-risk nulliparous pregnant woman asks a clinician about a scheduled CD, we are trained to thoroughly explore the reasons for the woman's request, including her intellectual, fact-based, concerns about labor and vaginal birth and her emotional reaction to the thought of a vaginal or cesarean birth. In this situation the clinician will provide information about the risks and benefits of vaginal versus CD. In the vast majority of situations, the pregnant woman will agree to attempting vaginal delivery. In one study of 458,767 births, only 0.2% of women choose a "maternal request cesarean delivery."[4]

After thorough counseling, if a woman and her clinician jointly agree to schedule a primary CD it will be the result of hours of intensive discussion, not an imprudent and hasty decision. In this case, the delivery is best characterized as a "maternal request cesarean delivery," not an "elective" CD.

Stop using the terms "elective termination of pregnancy" and "elective abortion"

Janiak and Goldberg have advocated for the elimination of the phrase elective abortion.[5] They write[5]:

> Support for abortion varies depending on the reason for the abortion—whether it is "elective" or "indicated." In the case of abortion, these terms generally differentiate between women seeking abortion for reasons of maternal or fetal health (an "indicated abortion") defined in contrast to women seeking abortion for other reasons (an "elective abortion"). We argue that such a distinction is impossible to operationalize in a just manner. The use of the phrase "elective abortion" promotes the institutionalization of a false hierarchy of need among abortion patients.

My experience is that pregnant women never seek an abortion based on whimsy. Most pregnant women who consider an abortion struggle greatly with the choice, using reason and judgment to arrive at their final decision. The choice to seek an abortion is always a difficult one, influenced by a constellation of hard facts that impact the woman's life. Using the term elective to describe an abortion implies a moral judgment and stigmatizes the choice to have an abortion. Janiak and Goldberg conclude by recommending the elimination of the phrase "elective abortion" in favor of the phrase "induced abortion."[5]

Time for change

Shockingly, in searching the *International Statistical Classification of Diseases and Related Health Problems,* 10th revision (ICD10), the word elective is most commonly used in the context of health services provided to pregnant women, including: elective induction of labor (Z34.90), elective cesarean delivery (O82), elective termination of pregnancy (Z33.2), and elective fetal reduction (Z031.30X0). In ICD10, other specialties do not describe the scope of their health services with the adjective elective.

There are many definitions and interpretations of elective. The most benign use of the word in the context of surgery is to contrast procedures that can be scheduled in the future with those that need to be performed urgently. In this context elective only refers to the timing, not the medical necessity, of the procedure. By contrast, describing a procedure as elective may signal that it is not medically necessary and is being performed based on the capricious preference of the patient or physician. Given the confusion and misunderstanding that may be caused by describing our important health services as "elective," I hope that we can permanently sunset use of the term. ●

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

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UPDATE Contraception

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Two new products and approval of extended use for an existing IUS will give women more contraceptive options and will impact clinician counseling

IN THIS ARTICLE

A vaginal ring that can be reused for up to 1 year and a progestin-only pill (POP) with a wider window for missed pills are 2 of the novel contraceptive products introduced to the market this year. In addition, an ongoing study of the levonorgestrel 52-mg intrauterine system (IUS) continues to provide evidence on its extended duration of use, now approved through 6 years.

The segesterone acetate (SA) and ethinyl estradiol (EE) vaginal ring (Annovera) is new among contraceptive options. Segesterone acetate is a novel progestin that can be used only via nonoral routes; it binds specifically to progesterone receptors without estrogenic or antiandrogen effects.[1] Unlike the etonogestrel and ethinyl estradiol ring (NuvaRing; for which generic products became available this past year), which is used for 1 cycle and then thrown away, the SA/EE ring is effective for 13 consecutive cycles. It does not require refrigeration when not in use.[2] Because a single ring can be used for 13 cycles, users in locations without laws that mandate a 12-month supply of pills, patches, and rings need less frequent visits to the pharmacy or clinic.

Progestin-only contraceptive pills are an important option for patients who desire hormonal contraception and have contraindications to estrogen, such as migraines with aura, cardiovascular risk factors, and being in the early postpartum period.[3] In the United States, current POPs contain norethindrone, which has a 3-hour window for missed pills[4]; a desogestrel-only pill available outside the United States has a 12-hour window.[5] Both are provided as a 28-day pill pack for continuous use, and both result in undesirable bleeding patterns in some users.

The prolonged half-life of drospirenone, another progestin, gives it the potential to increase reliability in the setting of missed or delayed pills and improve bleeding patterns. A new POP contraceptive contains drospirenone (Slynd) and is available in a 28-day pack with a 24-day supply of hormone and a 4-day supply of placebo; it provides a window for missed pill use similar to that for combined hormonal contraception (CHC) as well as a placebo period for a timed withdrawal bleed.[6,7]

Liletta is a well-known levonorgestrel 52-mg IUS that was first approved by the US Food and Drug Administration (FDA) in 2015. An ongoing clinical trial has been the basis for approval of this IUS for use in increasing durations, from 3 years initially to 4 and then 5 years. The newest data indicate efficacy up to 6 years.[8]

Combined hormonal vaginal system provides a year's contraception with an acceptable safety profile

Archer DF, Merkatz RB, Bahamondes L, et al. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: results of two multicentre, open-label, single-arm, phase 3 trials. Lancet Glob Health. 2019;7:e1054-e1064.

Gemzell-Danielsson K, Sitruk-Ware R, Creinin MD, et al. Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. Contraception. 2019;99:323-328.

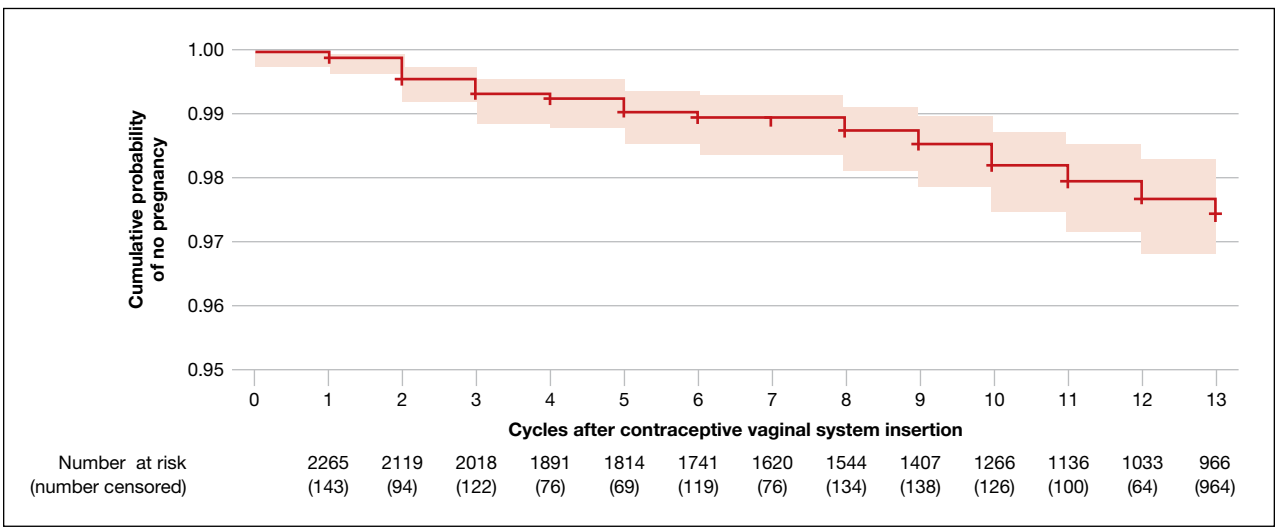
Archer and colleagues reported the results of 2 pivotal multicenter, open-label, phase 3 trials, which included 2,265 users, conducted to evaluate efficacy and return to menses or pregnancy after use of the 1-year (13 cycles) SA/EE contraceptive vaginal system (CVS).

Details of the efficacy study

The study included 1,130 women in a US-only study and 1,135 women in an international study with sites in the United States, Australia, Brazil, Chile, Dominican Republic, Finland, Hungary, and Sweden. Participants used the CVS for 21 days followed by a 7-day use-free interval for up to 13 consecutive cycles; they were instructed not to remove the CVS for more than 2 hours during the 21 days of use.

Primary and secondary efficacy outcomes were calculated using the Pearl Index and an intention-to-treat Kaplan-Meier life table, respectively. At the end of the study, users who desired not to continue hormonal contraception or to become pregnant were followed up for 6 months to evaluate return to menses or pregnancy.

FIGURE 1 Cumulative probability of no pregnancy with the SA/EE CVS over 13 cycles[2]



Cross marks indicate participant censoring; red shaded area indicates 95% confidence interval.
Abbreviation: SA/EE CVS, segesterone acetate and ethinyl estradiol contraceptive vaginal system.

CONTINUED ON PAGE 14

This letter first appeared in USA Today. The threat to women's health cannot be understated, which is why I share the same message with you.

Susan G. Komen founder:

New Cervical Cancer Screening Guidelines Dismiss Best Practices

Nancy G. Brinker

Founder, Susan G. Komen Foundation and The Promise Fund of Florida

The American Cancer Society issued at the end of July new guidelines for cervical cancer screening that call for fewer women to be tested and stand in direct opposition to recommendations from leading scientific organizations. As someone who has devoted their life to fighting for better and more accessible health care for women, I know that the disservice these changes will have on society, and woman specifically, could not come at a worse time.

The global health crisis we are living through right now is a stark reminder of just how dangerous a course of action the American Cancer Society's new guidelines may set in motion. In fact, while COVID-19 and cervical cancer are vastly different diseases, there are three important lessons related to the rollout and implementation of testing we should be learning in real time. The American Cancer Society's new guidelines ignore them all.

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Test like lives depend on it. They do.

First, if the experience of the coronavirus has taught us anything, it's that testing—widespread, science-driven and accessible testing—is crucial to understanding and combating disease. The more accurate testing we offer people, the better. Testing allows earlier detection and diagnoses and, when necessary, treatment. We know that while companies have been able to significantly ramp up production, the challenges people had in getting access to testing for COVID-19 in the early months likely intensified the crisis.

Where the current cervical cancer screening guidelines advise the Pap test for women starting at age 21, the new American Cancer Society guidelines advise delaying testing altogether until women turn 25, and then, preferably, solely with the HPV test every five years thereafter. This is despite the fact we know that the HPV test alone is less effective than co-testing along with the Pap test.

Not only does the American Cancer Society threaten the use of the life-saving Pap test, and recommend phasing it out entirely, but that four-year wait likely means fewer women cumulatively will be tested. If just having a cervix puts women at risk of a potentially fatal disease, it's a wait most woman may prefer to avoid.

Secondly, one of the most demoralizing responses to the current pandemic has been the disregard in some quarters for science, data, facts and the hard-won insights of the health care community. That the American Cancer Society, an organization I have long admired, should now fall into this category with its new guidelines is especially disheartening. Let's look at the science.

In a highly diverse and the largest cervical cancer screening study ever, the results of which were released in early July, co-testing with the Pap test and HPV test identified 94.1% of cervical cancer cases and 99.7% of pre-cancer cases in women who would be diagnosed within 12 months.

Co-testing remains the most effective strategy for detecting cervical cancer and precancer in women, but it is listed as an inferior choice by the new guidelines. Furthermore, that study demonstrates the use of HPV testing alone, which the American Cancer Society now recommends, misses twice as much cervical cancer as co-testing. We cannot disregard the science; we must follow it.

> If the pandemic has taught us anything, it's the more testing, the better. So why is the American Cancer Society recommending women get fewer tests?

Finally, mixed messages around coronavirus testing have sown confusion about who should get tested, and when. It has introduced uncertainty where there should be certainty and has led patients and even some health care professionals to question aspects of the system they rely on and trust. This isn't a result we want to replicate when it comes to cervical cancer screening.

Follow the science.

The American Cancer Society guidelines stand at odds with the previous guidelines that have helped drive a decrease in cervical cancer rates by 70% since the Pap test was introduced more than 50 years ago. They may introduce confusion about which tests to get and when, which in effect is building another barrier between women and the health care they deserve. The current challenges posed by testing in the time of COVID-19 has shown us just how dangerous such barriers can be.

An estimated 4,300 women will die in the United States from cervical cancer this year. Clarity drives trust and trust is essential to making progress in fighting this cancer.

With racial disparities in health care finally receiving the attention they deserve, and given what we are living through with the pandemic, it would be a tragedy if we do not at the very least learn from it. With a little tweak, George Santayana's admonition that "those who cannot remember the past are condemned to repeat it" can provide the most important insight of all. When it comes to the American Cancer Society's new guidelines on cervical cancer screening, it's not lessons from the past I'm worried we're ignoring, but lessons from the here and now.

A failure to acknowledge the lessons of this moment by loosening commonsense screening guidelines will almost surely reverse the progress we have made in combating cancer in recent years. If we allow this to be our future then we have learned nothing, and more women may die because of it.

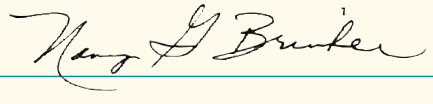

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TABLE 1 Characteristics of 4 participants with VTE during use of the 1-year SA/EE CVS in 2 phase 3 clinical trials[1]

Type of VTE	Cycle number	Risk factors
Pulmonary embolism	2	BMI >29.0 kg/m^2
Deep vein thrombosis	3	BMI >29.0 kg/m^2
Deep vein thrombosis	6	Factor V Leiden heterozygous
Cerebral venous thrombosis	7	Clotting evaluation not conducted. Smoking <10 cigarettes per day.

Abbreviations: BMI, body mass index; SA/EE CVS, segesterone acetate and ethinyl estradiol contraceptive vaginal system; VTE, venous thromboembolism.

Year-long effectiveness

The investigators reported an overall Pearl index of 2.98 (95% confidence interval [CI], 2.13–4.06) and a Kaplan-Meier life table cumulative efficacy rate of 97.5% (**FIGURE 1**, page 11), consistent with other recently approved CHC methods. Women from non-European sites, who primarily were US participants, had a Pearl Index of 3.25 (95% CI, 2.35–4.37), and participants from the European sites had a Pearl Index of 0.47 (95% CI, 0.03–2.07). Importantly, CVS removal had a significant impact on efficacy, with a Pearl Index of 5.98 (95% CI, 2.46–9.27) in users reporting CVS removals for longer than 2 hours, suggesting escape ovulation with improper use. The Pearl Index was highest in users aged 18 to 19 years and was not affected by body mass index (BMI), although 91% of users had a BMI of 29.0 kg/m^2 or lower.

There was no trend for a change in pregnancy risk across 13 cycles, providing evidence of CVS efficacy throughout a full year's use. The follow-up portion of the study included 290 users who were not continuing hormonal contraception at study end; all follow-up participants reported return to menses after method discontinuation.

Clinical safety data

To evaluate safety outcomes from clinical studies on the CVS containing SA/EE, Gemzell-Danielsson and colleagues analyzed

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The 13-cycle efficacy and general adverse events rates of the new SA/EE CVS are consistent with those of other CHCs. However, the efficacy and safety findings are not necessarily generalizable to all patients. Because users with a BMI greater than 29.0 kg/m^2 were excluded following 2 early VTE events in women with a BMI of 29.1 and 30.8 kg/m^2, only 9% of the phase 3 study population had a BMI greater than 29.0 kg/m^2. Clinicians may question whether the 1-year SA/EE CVS is an acceptable method for obese users. We know that EE causes similar changes in hemostatic factors regardless of oral or vaginal route,[9] but these studies as well as pharmacokinetic studies typically include relatively few participants. While studies demonstrate that the SA/EE CVS delivers EE 13 µg daily,[1] individual hormone absorption can vary. It is possible that the amount of EE in the CVS (17.4 mg) could, in a person predisposed to higher absorption, increase VTE risk. We do not know if this potential or actual risk is different for nonobese and obese users. To be fair, most of the EE-containing combined hormonal contraceptives were approved with study data that did not include obese women; the FDA first discussed the importance of including obese women in contraceptive approval studies in 2007.[10] Thus, we do not know if this CVS has a significantly higher VTE risk in obese users than other methods.

All available information is based on cyclic CVS use (28-day cycles with a 7-day use-free interval). No data are available on drug levels, safety, or efficacy over extended periods of continuous use with the same CVS. During counseling, special emphasis should be placed on the increased pregnancy risk for patients who remove the ring for more than 2 hours.

9 studies. Most of the data were derived from 2 phase 3, multicenter trials (as discussed above), with supporting evidence from 7 other studies.

Adverse events reported

Among 2,308 CVS users in the phase 3 trials, 87% reported at least 1 adverse effect, with most of mild or moderate severity. These included headache, 26%; nausea, 18%; vaginal discharge, 10%; and metrorrhagia, 7%. Overall, 12% of CVS users discontinued use due to an adverse effect. Two percent of users experienced severe adverse effects, including venous thromboembolism (VTE), allergic reaction, gallbladder disease, and spontaneous abortion.

In the US-only phase 3 trial, 2 VTE events occurred in the first 6 months in women with baseline BMI greater than 29.0 kg/m^2; therefore, enrollment of patients with a BMI greater than 29.0 kg/m^2 was halted and current users meeting that criteria were discontinued. Notably, no cases of VTE occurred in studies with a segesterone acetate–only CVS; this suggests that risk can be attributed to the estrogen component. Overall, 4 nonfatal VTEs occurred, all among the 1,536 women enrolled in the phase 3 trials (4 of 1,536 [0.3%]); at least 3 of these cases occurred in users with VTE risk factors (**TABLE 1**). The estimated VTE rate in CVS users with a BMI greater than 29.0 kg/m^2 is 10.8/10,000 women-years (95% CI, 8.9–13.1).

Complete expulsion of the CVS occurred in 7% of cycles and partial expulsion in 19.5% of cycles; users reported expulsion more frequently in the first cycle, most (about 70%) of which were partial expulsions. Of the laboratory values and vital signs studied, including weight, users had no clinically relevant changes from baseline.

New drospirenone pill is an effective POP option

Kimble T, Burke AE, Barnhart KT, et al. A 1-year prospective, open-label, single-arm, multicenter, phase 3 trial of the contraceptive efficacy and safety of the oral progestin-only pill drospirenone 4 mg using a 24/4-day regimen. Contracept X. 2020;2:100020.

Palacios S, Colli E, Regidor PA. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill. Acta Obstet Gynecol Scand. 2019;98:1549-1557.

In a prospective, single-arm, multicenter phase 3 trial in the United States, Kimble and colleagues evaluated the efficacy and safety of an oral drospirenone POP in a cyclic 24-day hormone/4-day placebo regimen. The trial included 1,006 users. No BMI cutoff was used, and about one-third of study participants were obese (BMI ≥30.0 kg/m^2). Women were instructed to take a missed tablet as soon as remembered if within 24 hours or with the next scheduled dose if more than 24 hours late.

Contraceptive effectiveness

The Pearl Index for nonbreastfeeding users aged 35 years or younger with pregnancies confirmed by a quantitative serum ß-human chorionic gonadotropin test (915 users) was 2.9 (95% CI, 1.5–5.1). Of note, 2 out of 15 on-treatment pregnancies were excluded from this calculation because of protocol site violations, as were 3 pregnancies that were unconfirmed. In the modified full analysis set of 915 users, 36% were obese (BMI ≥30 kg/m^2), and the Pearl Index was noted to be unaffected by BMI (**TABLE 2**, page 16).

While 61% of women reported adverse effects, more than 95% of these were mild or

FAST TRACK

Among 2,308 SA/EE CVS users in the phase 3 trials, 87% reported at least 1 adverse effect, with most of mild or moderate severity. Overall, 12% of women discontinued use due to an adverse effect.

TABLE 2 Pearl Index by BMI among women ≤35 years in a US drospirenone trial (modified full-analysis set), confirmed pregnancies[6]

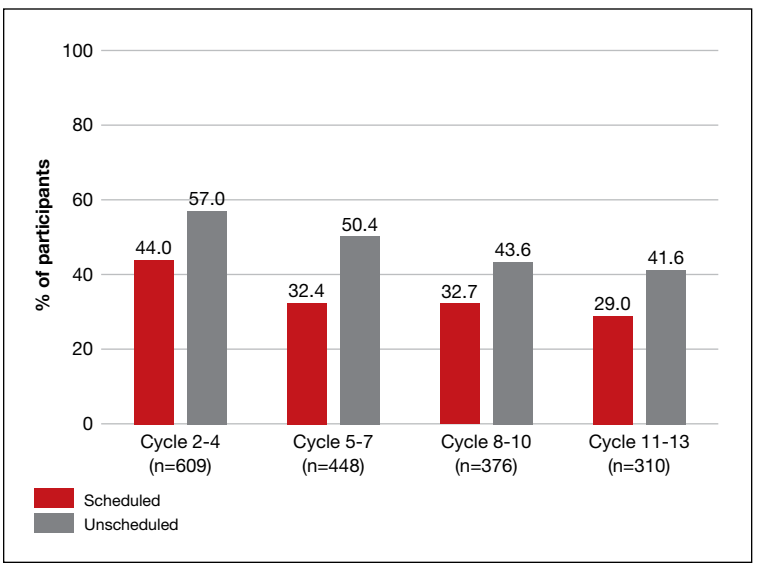
	BMI <30 kg/m² (n = 590)	BMI ≥30 kg/m² (n = 325)
Women with a pregnancy, n (%)	8 (1.4)	4 (1.2)
Exposure cycles	3,520	1,817
Pearl Index (95% CI)	3.0 (1.3–5.8)	2.9 (0.8–7.3)

Abbreviations: BMI, body mass index; CI, confidence interval.

moderate in intensity, including headache, nausea, dysmenorrhea, metrorrhagia, and breast pain. No VTE occurred. The frequency of hyperkalemia was 0.5%, and there was no evidence of hypotension, which is significant due to the antimineralocorticoid activity of drospirenone. All cases of hyperkalemia were considered mild, and all women were asymptomatic. There were no clinically relevant changes in body weight, gynecologic exam, or other laboratory values.

With increased cycles of use, the number of days with bleeding or spotting generally decreased and amenorrhea increased. However, in cycles 11 to 13, 41.6% of users still had unscheduled bleeding (reduced from 57.0% at cycles 2–4), and 29.0% had scheduled bleeding (decreased from 44% at cycles 2–4) (**FIGURE 2**). With these bleeding patterns, 86.2% of users agreed or strongly agreed that they were satisfied with the product.

FIGURE 2 Scheduled and unscheduled bleeding in a phase 3, multicenter 13-cycle trial of drospirenone 4 mg 24/4-day contraceptive regimen[6]



European multicenter study of drospironene

In a European investigation, Palacios and colleagues pooled and analyzed data from 2 phase 3 multicenter trials to assess the efficacy, tolerability, and safety of the same drospirenone-only pill (24 days of drospironene 4 mg and 4 days of placebo) in 1,571 users. No BMI cutoff was used, but overall only 71 participants (4.6%) were obese. One study included desogestrel 0.075 mg (in a regimen of 28 active pills) as a comparator for safety.

The overall Pearl Index for users 35 years or younger (1,251 users) was 1.0 (95% CI, 0.4–2.0). The "method failure Pearl Index" in users 35 years or younger, which included all pregnancies during "perfect medication cycles," was 1.3 (95% CI, 0.5–2.5).

The most common adverse effects were acne (6.6% in study 1 and 4.4% in study 2), headache (4.5% in study 1), and irregular bleeding (4.4% in study 2). No cases of VTE occurred; there was 1 case of asymptomatic hyperkalemia. Additional laboratory values and vital signs showed no significant changes. The trend in bleeding was similar to that in the US studies, but it is interesting to note that there were significantly lower rates of unscheduled bleeding or spotting in drospirenone users than in desogestrel users (67.9% vs 86.5%, respectively; $P<.001$).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In the US study, the higher Pearl Index compared with that found in the European study (2.9 vs 1.0) likely reflects an increased proportion of study participants with a BMI of 30 kg/m^2 or higher, a younger average age of participants, and a historical tendency toward better contraceptive efficacy in European than in US study participants. Kimble and colleagues' finding of a Pearl Index of 2.9 is similar to that seen with other CHCs and POPs, and the data from the US study are potentially more generalizable.

Among the 2,257 participants in 3 studies, 423 (19%) were obese. No VTE events occurred with drospirenone use, as compared with 4 events in the SA/EE CVS study with 2,308 participants in the phase 3 studies.

Historically, POPs were associated with more days of bleeding than CHCs and require stricter adherence to daily use within a narrow window for missed pills. The new drospirenone-only pill may provide women with more flexibility since it maintains contraceptive efficacy even with 24-hour delayed or missed-pill errors. Although intermenstrual bleeding rates are high, participants still had a very favorable assessment, and the profile may be more tolerable compared with other POPs. Clinicians prescribing this new POP should counsel patients that the cyclic regimen does not always result in regular bleeding patterns.

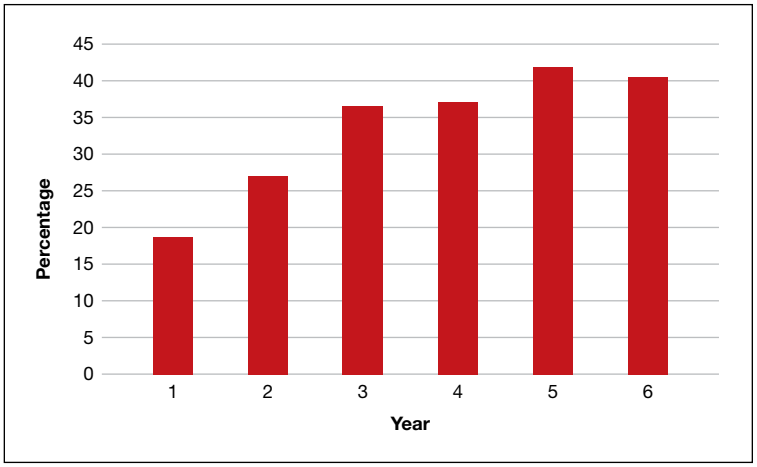
Evidence supports 6 years' use of a levonorgestrel 52-mg IUS

Westhoff CL, Keder LM, Gangestad A, et al. Six-year contraceptive efficacy and continued safety of a levonorgestrel 52 mg intrauterine system. Contraception. 2020;101:159-161.

Two levonorgestrel 52-mg IUS products are on the market, both of which were approved for 5 years of use. The ACCESS IUS study (A Comprehensive Contraceptive Efficacy and Safety Study of an IUS) is an ongoing phase 3 trial to assess the safety and efficacy of a levonorgestrel 52-mg IUS (Liletta) for up to 10 years of use in US women. Westhoff and colleagues presented the data used for this IUS to gain approval for 6 years of use as of October 2019. The report included safety information for all users, with use exceeding 8 years in 122 participants.

In year 6 of the ongoing trial, there were no on-treatment pregnancies with a 6-year life table pregnancy rate of 0.87 (95% CI, 0.44–1.70). Forty percent of users reported amenorrhea in the 90 days preceding the end of year 6, consistent with prior data after 3 years of use (**FIGURE 3**). The most common adverse effects over 6 or more years of use were bacterial vulvovaginal infections and urinary tract infections.

FIGURE 3 Amenorrhea rates over 6 years in users of the levonorgestrel 52-mg IUS[8,11 a]



Abbreviation: IUS, intrauterine system.

[a]Amenorrhea defined as no bleeding or spotting in the preceding 90 days; data evaluated for 90 days before end of year.

CONTINUED ON PAGE 46

BLACK WOMEN'S HEALTH IMPERATIVE

ACS Guidelines Will Jeopardize Lives and Severely Limit Disease Detection

We have made significant progress in the fight against cervical cancer over the past several decades, yet, alarmingly, rates are beginning to increase among certain populations.

Black women in the United States die from cervical cancer at more than two times the rate of white women. Also, because of delays in screening, Black women are more likely to be diagnosed with advanced cervical cancer than any other racial group.

The Black Women's Health Imperative (BWHI) is the only national non-profit organization dedicated to advancing health equity and social justice for Black women, across lifespan, through policy, advocacy, education, research and leadership development. The organization identifies the most pressing health issues that affect the nation's 22 million Black women and girls and invests in evidence-based strategies and best-in-class organizations to accomplish its goals.

At a time when the US health care community should be reaffirming its commitment to preventing cervical cancer, the **American Cancer Society (ACS) has released new screening guidelines that fail to preserve access to the most accurate and effective cervical cancer screening options** and threatens to put lives at risk.

The new guidelines from the ACS recommend against continued routine use of the Pap test, instead suggesting that women ages 25-65 undergo primary HPV testing every five years. Additionally, the guidelines remove a recommendation to screen women under age 25 altogether. These changes represent **a staggering departure from established**

current clinical practice and screening guidelines from other professional societies.

Co-testing with the Pap test and HPV test together is the preferred screening strategy in the United States among both healthcare providers and women, and it has greatly contributed to saving lives. Real-world data demonstrated through several large domestic studies have found that co-testing detects more pre-cancerous lesions and cervical cancer cases than either test alone. Additionally, one study has shown that screening with the HPV test alone, as the ACS recommends, **could miss a cancer diagnosis in 20 percent of women**.

The ACS guidelines admit that **Black women have significantly higher rates of cervical cancer**, yet by limiting screening options these guidelines will widen the racial disparity gap even further. Health care disparities among Black women result from systemic racism, less access to health care, and receiving lower-quality care as compared with white women. Black women are passionate about their health and actively involved in caring for themselves. But many must make decisions to forgo or delay screenings due to concerns about cost and the lack of health care coverage. The current "one- size-fits-all" approach fails to consider the needs of each individual and it ignores the science. This is why access to affordable and comprehensive screening is imperative in ensuring the early detection and treatment of cervical cancer in Black women.

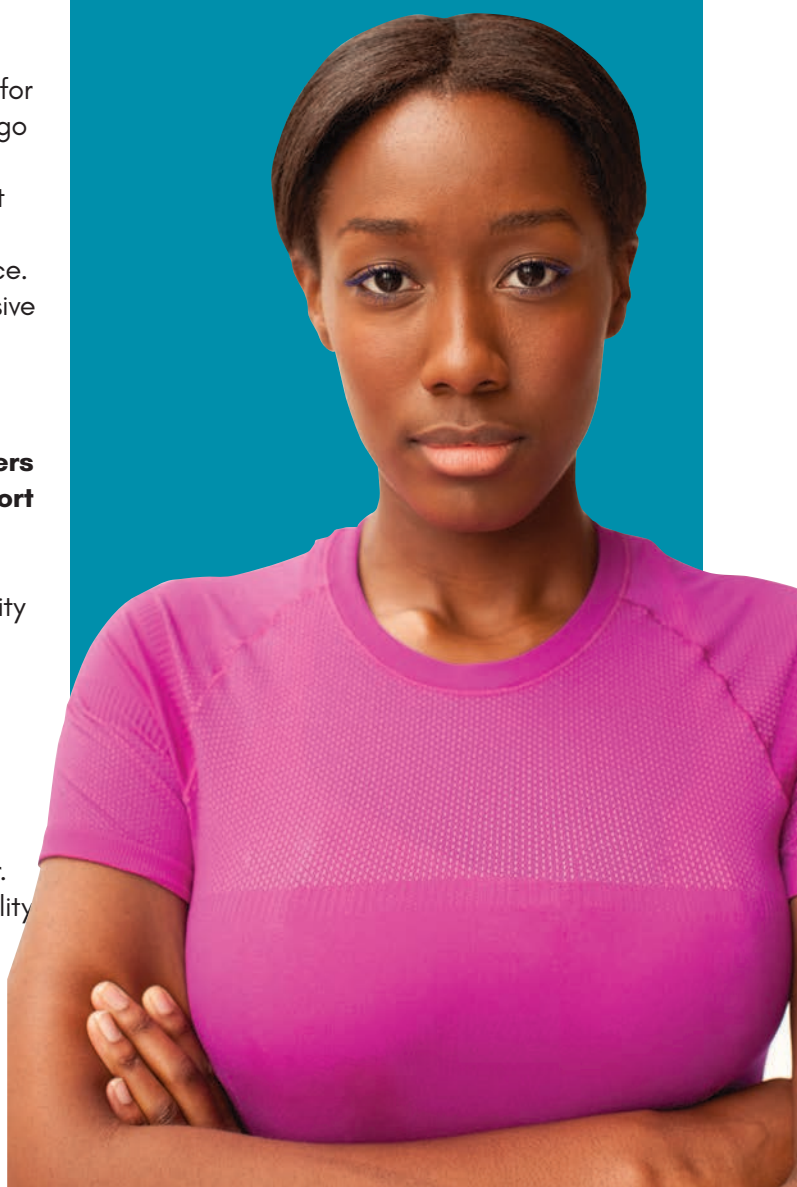
The ACS owes women and healthcare providers an answer as to why they would remove support for trusted testing options when preventive healthcare is already fragile due to the COVID-19 pandemic. They have lost sight of their responsibility to put choice, access, and proven science at the forefront, instead making decisions that are odds with their stated mission to "lead the fight for a world without cancer."

We strongly urge the ACS to reconsider their new guidelines and vision for the future. Far too many women die needlessly from cervical cancer. However, we have the tools, the data and the ability to make a difference, especially in this country. **We invite ACS to join us in preserving all options for women so we can eradicate this disease together.** ♀

Black women in the US die from cervical cancer more than

2x

the rate of white women.



BREAST HEALTH

How ObGyns can best work with radiologists to optimize screening for patients with dense breasts

Discussions with patients around breast cancer screening typically rest on the shoulders of ObGyns. When a patient is informed she has dense breasts, what should your dialogue include, and what resources are available to you?

Elizabeth Etkin-Kramer, MD; DaCarla M. Albright, MD; and JoAnn Pushkin

IN THIS ARTICLE

If your ObGyn practices are anything like ours, every time there is news coverage of a study regarding mammography or about efforts to pass a breast density inform law, your phone rings with patient calls. In fact, every density inform law enacted in the United States, except for in Illinois, directs patients to their referring provider—generally their ObGyn—to discuss the screening and risk implications of dense breast tissue.

The steady increased awareness of breast density means that we, as ObGyns and other primary care providers (PCPs), have additional responsibilities in managing the breast health of our patients. This includes guiding discussions with patients about what breast density means and whether supplemental screening beyond mammography might be beneficial.

As members of the Medical Advisory Board for DenseBreast-info.org (an online educational resource dedicated to providing breast density information to patients and health care professionals), we are aware of the growing body of evidence demonstrating improved detection of early breast cancer using supplemental screening in dense breasts. However, we know that there is confusion among clinicians about how and when to facilitate tailored screening for women with dense breasts or other breast cancer risk factors. Here we answer 6 questions focusing on how to navigate patient discussions around the topic and the best way to collaborate with radiologists to improve breast care for patients.

Dr. Etkin-Kramer is Assistant Professor, Florida International University School of Medicine, and Founder, Yodeah.org, Miami Beach, Florida.

Dr. Albright is Associate Professor, Associate Dean for Student Affairs and Wellness, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania.

Ms. Pushkin is Executive Director, DenseBreast-info.org.

Dr. Etkin-Kramer reports being an unpaid medical advisory board member for Bright Pink and the founder of Yodeah.org. Dr. Albright reports being a speaker for and serving on the medical advisory board for Hologic, Inc. Ms. Pushkin reports no financial relationships relevant to this article.

doi: 10.12788/obgm.0040

Play an active role

1. What role should ObGyns and PCPs play in women's breast health?

Elizabeth Etkin-Kramer, MD: I am a firm believer that ObGyns and all women's health providers should be able to assess their patients' risk of breast cancer and explain the process for managing this risk with

their patients. This explanation includes the clinical implications of breast density and when supplemental screening should be employed. It is also important for providers to know when to offer genetic testing and when a patient's personal or family history indicates supplemental screening with breast magnetic resonance imaging (MRI).

DaCarla M. Albright, MD: I absolutely agree that PCPs, ObGyns, and family practitioners should spend the time to be educated about breast density and supplemental screening options. While the exact role providers play in managing patients' breast health may vary depending on the practice type or location, the need for knowledge and comfort when talking with patients to help them make informed decisions is critical. Breast health and screening, including the importance of breast density, happen to be a particular interest of mine. I have participated in educational webinars, invited lectures, and breast cancer awareness media events on this topic in the past.

Join forces with imaging centers

2. How can ObGyns and radiologists collaborate most effectively to use screening results to personalize breast care for patients?

Dr. Etkin-Kramer: It is important to have a close relationship with the radiologists that read our patients' mammograms. We need to be able to easily contact the radiologist and quickly get clarification on a patient's report or discuss next steps. Imaging centers should consider running outreach programs to educate their referring providers on how to risk assess, with this assessment inclusive of breast density. Dinner lectures or grand round meetings are effective to facilitate communication between the radiology community and the ObGyn community. Finally, as we all know, supplemental screening is often subject to copays and deductibles per insurance coverage. If advocacy groups, who are working to eliminate these types of costs, cannot get insurers to waive these payments, we need a less expensive self-pay option.

Dr. Albright: I definitely have and encourage an open line of communication between my practice and breast radiology, as well as our breast surgeons and cancer center to set up consultations as needed. We also invite our radiologists as guests to monthly practice meetings or grand rounds within our department to further improve access and open communication, as this environment is one in which greater provider education on density and adjunctive screening can be achieved.

Know when to refer a high-risk patient

3. Most ObGyns routinely collect family history and perform formal risk assessment. What do you need to know about referring patients to a high-risk program?

Dr. Etkin-Kramer: It is important as ObGyns to be knowledgeable about breast and ovarian cancer risk assessment and genetic testing for cancer susceptibility genes. Our patients expect that of us. I am comfortable doing risk assessment in my office, but I sometimes refer to other specialists in the community if the patient needs additional counseling. For risk assessment, I look at family and personal history, breast density, and other factors that might lead me to believe the patient might carry a hereditary cancer susceptibility gene, including Ashkenazi Jewish ancestry.[1] When indicated, I check lifetime as well as short-term (5- to 10-year) risk, usually using Breast Cancer Surveillance Consortium (BCSC) or Tyrer-Cuzick/International Breast Cancer Intervention Study (IBIS) models, as these include breast density.

I discuss risk-reducing medications. The US Preventive Services Task Force recommends these agents if my patient's 5-year risk of breast cancer is 1.67% or greater, and I strongly recommend chemoprevention when the patient's 5-year BCSC risk exceeds 3%, provided likely benefits exceed risks.[2,3] I discuss adding screening breast MRI if lifetime risk by Tyrer-Cuzick exceeds 20%. (Note that Gail and BCSC models are not recommended to be used to determine risk for purposes of

FAST TRACK

Maintain close relationships with radiologists/imaging centers so that your questions can be answered quickly and appropriately

supplemental screening with MRI as they do not consider paternal family history nor age of relatives at diagnosis.)

Dr. Albright: ObGyns should be able to ascertain a pertinent history and identify patients at risk for breast cancer based on their personal history, family history, and breast imaging/biopsy history, if relevant. We also need to improve our discussions of supplemental screening for patients who have heterogeneously dense or extremely dense breast tissue. I sense that some ObGyns may rely heavily on the radiologist to suggest supplemental screening, but patients actually look to ObGyns as their providers to have this knowledge and give them direction.

Since I practice at a large academic medical center, I have the opportunity to refer patients to our Breast Cancer Genetics Program because I may be limited on time for counseling in the office and do not want to miss salient details. With all of the information I have ascertained about the patient, I am able to determine and encourage appropriate screening and assure insurance coverage for adjunctive breast MRI when appropriate.

FAST TRACK

Be familiar with the breast screening orders your institution's EHR offer; they may be helpful to avoid additional scripts down the line

Consider how you order patients' screening to reduce barriers and cost

4. How would you suggest reducing barriers when referring patients for supplemental screening, such as MRI for high-risk women or ultrasound for those with dense breasts? Would you prefer it if such screening could be performed without additional script/referral? How does insurance coverage factor in?

Dr. Etkin-Kramer: I would *love* for a screening mammogram with possible ultrasound, on one script, to be the norm. One of the centers that I work with accepts a script written this way. Further, when a patient receives screening at a freestanding facility as opposed to a hospital, the fee for the supplemental screening may be lower because they do not add on a facility fee.

Dr. Albright: We have an order in our electronic health record that allows for screening mammography but adds on diagnostic mammography/bilateral ultrasonography, if indicated by imaging. I am mostly ordering that option now for all of my screening patients; rarely have I had issues with insurance accepting that script. As for when ordering an MRI, I always try to ensure that I have done the patient's personal risk assessment and included that lifetime breast cancer risk on the order. If the risk is 20% or higher, I typically do not have any insurance coverage issues. If I am ordering MRI as supplemental screening, I typically order the "Fast MRI" protocol that our center offers. This order incurs a $299 out-of-pocket cost for the patient. Any patient with heterogeneously or extremely dense breasts on mammography should have this option, but it requires patient education, discussion with the provider, and an additional cost. I definitely think that insurers need to consider covering supplemental screening, since breast density is reportable in a majority of the US states and will soon be the national standard.

Pearls for guiding patients

5. How do you discuss breast density and the need for supplemental screening with your patients?

Dr. Etkin-Kramer: I strongly feel that my patients need to know when a screening test has limited ability to do its job. This is the case with dense breasts. Visuals help; when discussing breast density, I like the images supplied by DenseBreast-info.org (**FIGURE**, page 24). I explain the two implications of dense tissue:

- First, dense tissue makes it harder to visualize cancers in the breast—the denser the breasts, the less likely the radiologist can pick up a cancer, so mammographic sensitivity for extremely dense breasts can be as low as 25% to 50%.
- Second, high breast density adds to the risk of developing breast cancer. I explain that supplemental screening will pick up additional cancers in women with dense breasts. For example, breast ultrasound will

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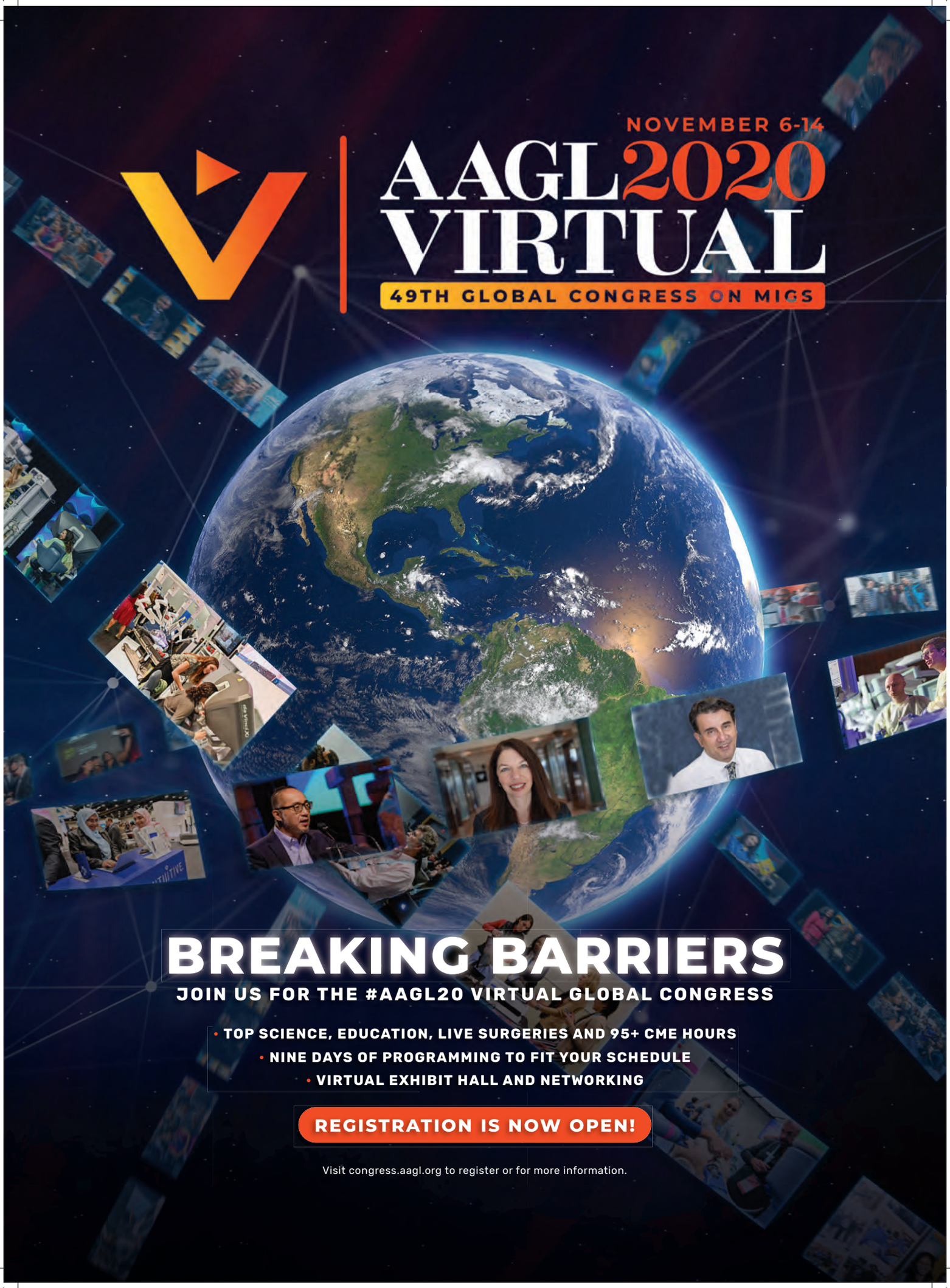

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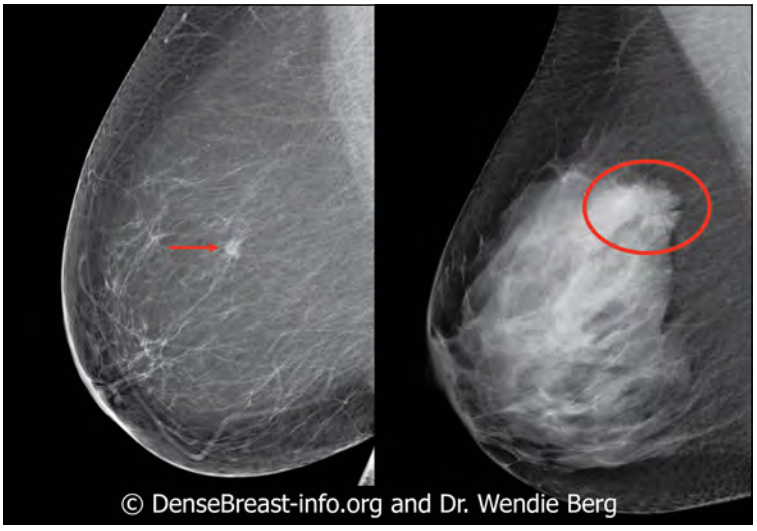
FIGURE Fatty vs dense breast tissue



Cancers are difficult to detect in dense tissue (right) using mammography. *Courtesy of DenseBreast-Info.org and Wendie Berg, MD, PhD.*

FAST TRACK

Patient discussions should include the associated risks of cancer with dense breasts

pick up about 2-3/1000 additional breast cancers per year and MRI or molecular breast imaging (MBI) will pick up much more, perhaps 10/1000.

MRI is more invasive than an ultrasound and uses gadolinium, and MBI has more radiation. Supplemental screening is not endorsed by ACOG's most recent Committee Opinion from 2017;[4] however, patients may choose to have it done. This is where shared-decision making is important.

I strongly recommend that all women's health care providers complete the CME course on the DenseBreast-info.org website. "Breast Density: Why It Matters" is a certified educational program for referring physicians that helps health care professionals learn about breast density, its associated risks, and how best to guide patients regarding breast cancer screening.

Dr. Albright: When I discuss breast density, I make sure that patients understand that their mammogram determines the density of their breast tissue. I review that in the higher density categories (heterogeneously dense or extremely dense), there is a higher risk of missing cancer, and that these categories are also associated with a higher risk of breast cancer. I also discuss the potential need for supplemental screening, for which my institution primarily offers Fast MRI. However, we can offer breast ultrasonography instead as an option, especially for those concerned about gadolinium exposure. Our center offers either of these supplemental screenings at a cost of $299. I also review the lack of coverage for supplemental screening by some insurance carriers, as both providers and patients may need to advocate for insurer coverage of adjunct studies.

Educational resources

6. What reference materials, illustrations, or other tools do you use to educate your patients?

Dr. Etkin-Kramer: I frequently use handouts printed from the DenseBreast-info.org website, and there is now a brand new patient fact sheet that I have just started using. I also have an example of breast density categories from fatty replaced to extremely dense on my computer, and I am putting it on a new smart board.

Dr. Albright: The extensive resources available at DenseBreast-info.org can improve both patient and provider knowledge of these important issues, so I suggest patients visit that website, and I use many of the images and visuals to help explain breast density. I even use the materials from the website for educating my resident trainees on breast health and screening. ●

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Urethral bulking agents for SUI: Rethinking their indications

Rising interest in alternatives to sling procedures and increasing evidence of successful outcomes for urethral bulking agents make them a potential primary treatment option for patients with SUI

Mallorie L. Hoover, DO, and Mickey Karram, MD

Stress urinary incontinence (SUI) is the involuntary loss of urine with increased intra-abdominal pressure, such as with physical exertion, sneezing, or coughing.[1] Currently, the gold standard treatment for SUI is surgical repair with the use of a synthetic midurethral sling (MUS), based on long-term data that support its excellent efficacy and durability. The risk-benefit balance of MUS continues to be scrutinized, however, with erosions and pain poorly studied and apparently underreported.

The medical-legal risks associated with the MUS are a significant concern and have led many patients to reconsider this option for their condition. Many other countries (United Kingdom, Australia, New Zealand, and European Union) are now re-evaluating the use of the MUS.[2] In the United Kingdom, for example, the National Institute for Health and Care Excellence (NICE) Guideline advises considering the MUS only when another surgical intervention is not suitable for the patient.[3]

In light of the heightened skepticism surrounding the MUS, interest has increased in the use of urethral bulking agents. These agents consist of a material injected into the wall of the urethra to improve urethral coaptation in women with SUI.[4]

A brief history of bulking agents

In 1938, Murless first reported the injection of sodium morrhuate for the management of urinary incontinence.[4] Other early bulking agents introduced in the 1950s and 1960s included paraffin wax and sclerosing agents. Subsequently, Teflon, collagen, and autologous fat, among other agents, were found to be efficacious for augmenting urethral coaptation; however, only collagen initially demonstrated acceptable safety.[5]

Contigen (bovine dermal collagen cross-linked with gluteraldehyde) was approved as a bulking agent by the US Food and Drug Administration (FDA) in 1993; however, the manufacturing of bovine collagen was halted in 2011. Contigen was the only *nonpermanent* biodegradable urethral bulking agent, and its use required skin testing prior to use, as 2% to 5% of women experienced allergic reaction.[4]

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Dr. Karram reports that he is a consultant to Coloplast and Contura. Dr. Hoover reports no financial relationships relevant to this article.

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Presently, 3 particle-based urethral bulking agents are FDA approved for marketing in the United States: Macroplastique (Laborie Medical Technologies), Coaptite (Boston Scientific), and Durasphere (Coloplast). In addition, Bulkamid (Contura), which was approved earlier this year, is a nonparticulate agent composed of a nonresorbable polyacrylamide hydrogel.[5]

Indications for use

According to the FDA premarket approvals (PMAs) for the particle-based urethral bulking agents, their use is indicated for adult women with SUI primarily due to intrinsic sphincter deficiency (ISD).[6] The PMA indication for the nonparticulate agent, however, allows it to be used for SUI as well as SUI-predominant mixed urinary incontinence (MUI) due to ISD.[7] Traditionally, ISD is defined by urodynamic criteria that includes a maximal urethral closure pressure less than 20 to 25 cm of water and/or a Valsalva leak point pressure of less than 60 cm of water.[4]

The American Urological Association (AUA) guideline lists bulking agents as an option for women who do not wish to pursue invasive surgical intervention for SUI, are concerned about lengthier recovery after surgery, or have previously undergone anti-incontinence procedures with suboptimal results.[8] In general, most urologists and urogynecologists who perform urethral bulking agree with the AUA guideline.

Perceptions of bulking agents have shifted

Urethral bulking agents traditionally have been thought of as a "salvage therapy." Perceived indications for these agents include use in women with persistent SUI after more invasive treatment options or in women who were medically fragile and thus could not undergo a more invasive procedure.[9] As mentioned, however, circumstances related to mesh use have shifted the current perception of indications for urethral bulking agents from salvage therapy only to use as a possible first-line treatment in the appropriately selected patient.[9]

Recent data that note improved durability and patient satisfaction, as well as better appreciation of the fact that, if the bulking agent fails, a synthetic sling procedure still can be performed without significant concerns, have contributed to this shift in intervention strategy.[10,11] There also has been the perception that urethral bulking agents should not be considered in women who have urethral mobility. However, studies have shown that outcomes are not significantly different in patients with urethral mobility compared with those with a fixed urethra.[11]

Types of bulking agents

The ideal bulking agent should be made of a material that is biocompatible—with low host reactivity, low carcinogenic potential, low risk of migration—and easy to administer.[5] Currently available bulking agents are classified as particulate and nonparticulate agents. The **TABLE** on page 28 provides summary details of the available agents FDA approved for use.

Particulate bulking agents

Durasphere, approved by the FDA in 1999, is composed of carbon-coated zirconium oxide in a water-based and beta-glucan carrier. The first generation of this agent had particles that ranged in size from 212 to 500 µm and required an 18-gauge needle for injection.[4] The second-generation preparation has a smaller particle size, ranging from 90 to 212 µm, which permits injection with a smaller needle, typically 20 gauge.[4] Theoretically, the larger bead size reduces the risk of migration as particles larger than 80 µm cannot be engulfed by macrophages.[4]

Coaptite is a calcium hydroxylapatite–based product approved by the FDA in 2005. The carrier media is composed of sodium carboxymethylcellulose, sterile water, and glycerin. The particle size ranges from 75 to 125 µm, with an average of 100 µm.[5] This synthetic material historically has been used in orthopedics and dental applications. The aqueous gel carrier dissipates over months,

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

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

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

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

[‡§]Cologuard specificity: 87% overall specificity, excluding CRC and advanced adenomas, and including all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy. There was 90% specificity in participants with no lesions biopsied on colonoscopy.[1]

[‡‖]Negative predictive value (NPV) is defined as the probability that disease is absent in those with a negative result; it is highly dependent on the prevalence of the disease. NPV was derived from the patient population evaluated in the Imperiale et al publication.[1]

Reference: 1. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014;370(14):1287-1297.

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TABLE Injectable urethral bulking agents available in North America

Agent	Material	FDA approval date	Needle gauge	Cystoscope
Durasphere	Pyrolytic carbon-coated graphite beads	1999	18, 20 gauge	Standard cystoscope
Coaptite	Calcium hydroxylapatite	2005	21 gauge	Standard cystoscope
Macroplastique	Polydimethylsiloxane macroparticle	2006	18, 20 gauge	Proprietary delivery system
Bulkamid	Polyacrylamide hydrogel	2020	23 gauge	Proprietary delivery system

resulting in tissue growth; thereafter, the particulate beads slowly degrade.[12]

Macroplastique, a polydimethylsiloxane compound, was approved by the FDA in 2006. It has a long history of use primarily in Europe where it has been used since 1991. It is composed of a nonbiodegradable silicone (polydimethylsiloxane) elastomer suspended in a water-soluble gel. The initial composition was of particles that ranged in size from 5 to 400 µm, with 25% of the particles smaller than 50 µm. Because of the large number of particles smaller than 50 µm, there were concerns for migration.[5] The agent's current composition contains particles that range from 120 to 600 µm, with an average particle size of 140 µm.[4]

Nonparticulate bulking agent

Bulkamid has been available in Europe since 2003 and was FDA approved in January 2020. It is the only available nonparticulate urethral bulking agent; it is composed uniquely of a nonresorbable polyacrylamide hydrogel made of cross-linked 2.5% polyacrylamide and water. Its bulking effect is achieved through the actual volume of hydrogel injected, which integrates with host tissue by vessel ingrowth, suggestive of a persistent durable effect. Because Bulkamid contains no particles or crystals, the theoretical risk of migration is mitigated.[4]

The urethral bulking technique

The basic technique for urethral bulking is similar for all agents, with nuances in technique for each agent.

The procedure typically begins with placement of 2% lidocaine gel in the urethra for 5 to 10 minutes. The disposable needle is primed with the agent.[4] For Durasphere, an 18- or 21-gauge rigid needle is used; for Coaptite, a 21-gauge rigid side injecting needle called the SideKick is used; and for Macroplastique, an 18- or 20-gauge rigid needle is used.[4] Bulkamid administration requires the use of a special 23-gauge needle. Durasphere and Coaptite are delivered via a standard cystoscope.[4] Macroplastique requires a proprietary delivery system[4] (**FIGURE 1**, page 30). Bulkamid has a proprietary urethroscope and rotatable sheath to guide accuracy of injection (**FIGURE 2**, page 30).[4]

After the needle is primed and the delivery device placed into the urethra, the injection site is selected, approximately 1.5 to 2 cm from the bladder neck. The needle is introduced into the suburethral tissue at a 30- to 45-degree angle.

The injection site varies by agent. The 4 and 8 o'clock positions are recommended for Coaptite and Durasphere, while the 2, 6, and 10 o'clock positions are recommended for Macroplastique. For Bulkamid, the recommendation is to create 3 cushions at the 2, 6, and 10 o'clock positions.[13] Regardless of the agent used, the bulking is easily visualized and should result in the various sites meeting in the midline (**FIGURE 3**, page 32).

Evidence-based outcomes

The published data on outcomes of urethral bulking treatments have used inconsistent measures of efficacy. Most of the FDA trials used subjective success calculated with use of the Stamey Urinary Incontinence Scale (Stamey Grade) and validated questionnaires

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FIGURE 1 Proprietary injection system for Macroplastique urethral bulking agent

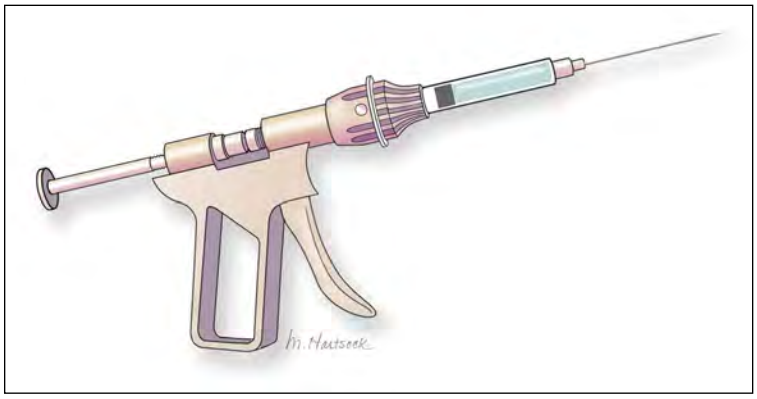
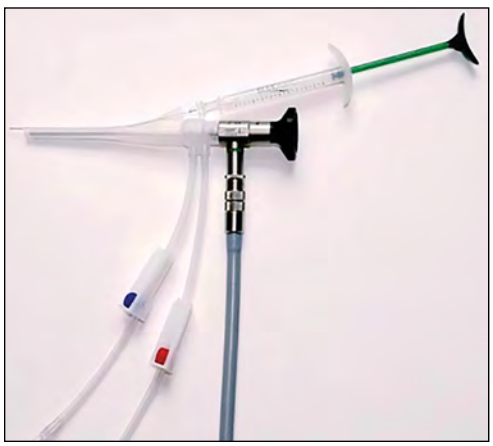


FIGURE 2 Proprietary injection system for Bulkamid urethral bulking agent



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as well as objective data collected via voiding diaries and pad tests.[4]

In 2007, a multicenter prospective randomized controlled trial (RCT) compared Coaptite with Contigen treatment and found that 63.4% versus 57.0% of patients, respectively, experienced an improvement on the Stamey Urinary Incontinence Scale at 12-month follow-up.[14]

A prospective multicenter RCT in 2009 was conducted to test the durability and efficacy of Macroplastique treatment at 12-month follow-up.[15] The authors noted that at 12 months, 62% of treated women reported significant improvement.[15] Further, a systematic review and meta-analysis of the literature (1990–2010) on Macroplastique use was published in 2013.[16] Data from 958 patients from 23 cohorts were analyzed in a random-effects model for 3 time periods: short term (less than 6 months), mid term (6–12 months), and long term (>18 months). Cure/dry rates were reported for short, mid, and long-term follow-up as 43% (95% confidence interval [CI], 33%–54%), 37% (95% CI, 28%–46%), and 36% (95% CI, 27%–46%), respectively.[16]

The newest bulking product in the United States, Bulkamid, has been available for use in Europe since 2003.[17] In a 3-year follow-up of a prospective nonrandomized single-site study, 212 of 256 (82.8%) participants were subjectively cured or had significant improvement in SUI or MUI, and this result was maintained until the end of the study period (a median of 38 months).[10] In 2014, an 8-year follow-up of 24 women was published.[18] Subjectively, 44% of the women reported cure or significant improvement, and 11 women who presented for objective evaluation all had polyacrylamide hydrogel visible on vaginal ultrasound.[18]

In addition, an RCT published in 2020 compared surgery with tension-free vaginal tape (TVT) and Bulkamid use in 224 women with SUI. At the 12-month follow-up, TVT was found to be more effective than Bulkamid; the median visual analog scale score for satisfaction was 99 for the TVT-treated group and 85 for the Bulkamid-treated patients.[11] Additionally, a cough stress test was negative in 95.0% and 66.4% of participants, respectively, but reoperations occurred only in patients who received the TVT procedure (n = 6). The authors concluded that while TVT treatment provided higher satisfaction rates than did Bulkamid, all major perioperative and follow-up complications were associated with TVT use. The study is ongoing and will eventually report 3-year outcomes.[11]

According to a 2017 Cochrane Review on urethral bulking, treatments with all 3 of the particulate bulking agents resulted in improvements that were no more or less effective

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ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

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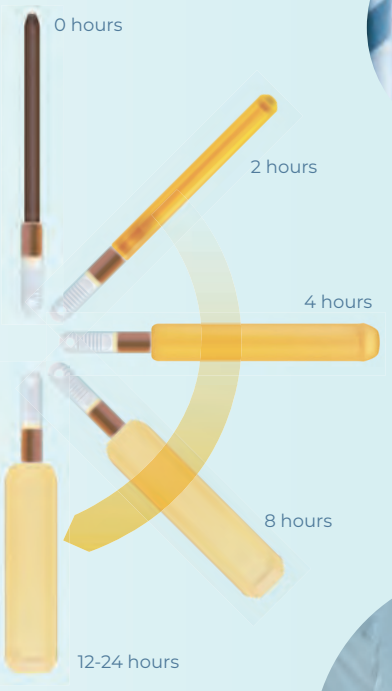

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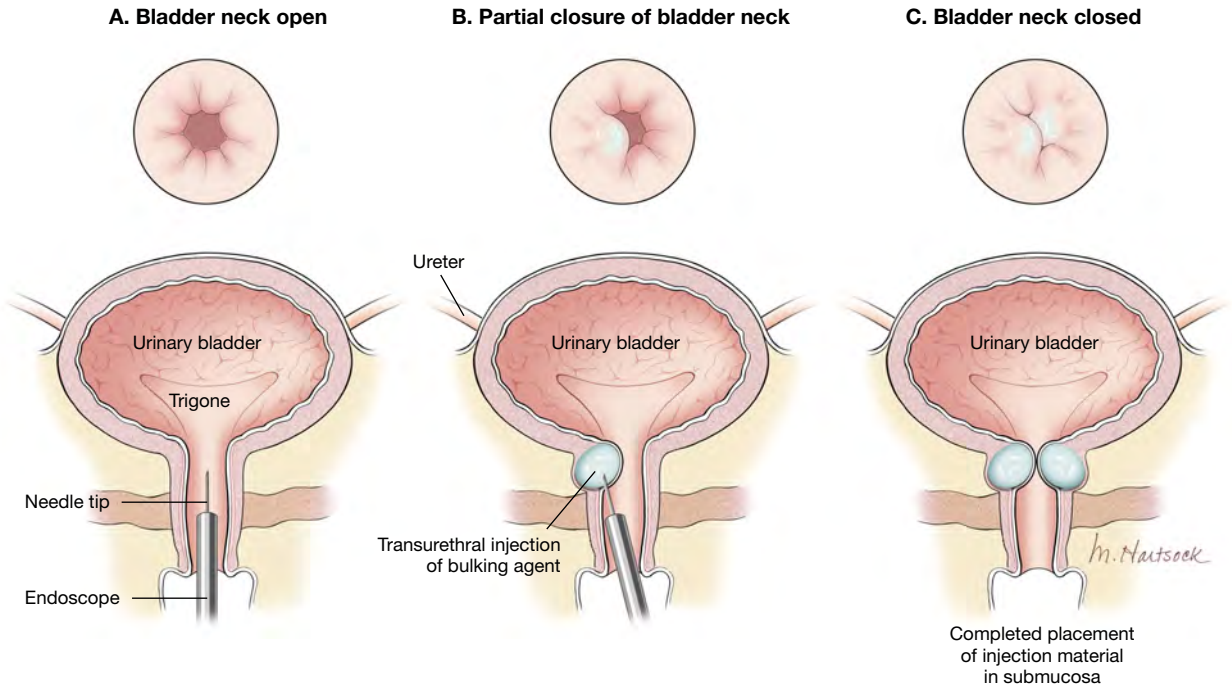
FIGURE 3 Urethral bulking agent injection results in closure of the bladder neck



than Contigen treatment. The review failed to include publications on Bulkamid treatment.[19]

Complications and safety issues

Adverse events. Reported adverse effects associated with urethral bulking include mild pain, transient urinary retention (typically resolving within 1–2 days after injection), dysuria, hematuria, and urinary tract infection (UTI).[4,12]

In a 12-month RCT involving 355 women treated with Durasphere or bovine collagen, adverse events were reported in 178 Durasphere-treated women; dysuria (24.7%) and temporary urinary retention (16.9%) were the most commonly reported adverse events.[20]

An RCT of Coaptite injection (n = 296) found that temporary urinary retention (41%) was the most common adverse event.[14]

In a 12-month comparative study of Macroplastique versus Contigen (n = 122), UTI was reported as the most common adverse event (23.8%), followed by dysuria (9%) and urgency (9%).[15] In addition, in a meta-analysis involving 958 patients in 23 cohorts, Ghoniem and Miller reported that the median rates for adverse events were temporary dysuria, 50%; hematuria, 45%; urge incontinence, 7%; temporary urinary retention, 7%; and UTI, 3%.[16]

A 3-year summary outcome of 256 patients who received Bulkamid injection reported that only 1 patient developed infection, abscess, or allergic reaction at the injection site and 1 patient had a UTI.[10] In an 8-year follow-up of patients who received Bulkamid injection, 1 patient experienced stranguria and 7 patients had recurrent cystitis.[18]

It appears that transient dysuria, urgency, and urinary retention occur more frequently after urethral bulking with particulate agents.[12]

Complications. Few delayed but serious complications after urethral bulking have been reported, including suburethral abscess, urethral prolapse, and particle migration.[4] Cases of urethral prolapse have been reported with both Coaptite and Durasphere.

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ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

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Notably, all cases of urethral prolapse occurred in patients with a history of pelvic surgery and/or previous urethral bulking.[21,22] Cases also have been reported of Durasphere carbon bead particles migrating to regional and distant lymph nodes, and pseudoabscess also has been reported.[12,23] A single case of periurethral abscess was reported after Bulkamid injection in a patient who had prior vaginal hysterectomy and a transobturator tape procedure after a total vaginal mesh repair.[24]

Bulking agent use: Time to go mainstream?

Historically, urethral bulking agents have had limited utility, largely due to the inaccurate and unsubstantiated perceptions of them being indicated only in women with ISD and a well-supported urethra. More recently, urethral bulking agents are commonly being used in patients who: have recurrent SUI after a surgical intervention, have infrequent but bothersome SUI symptoms, are not ideal candidates to undergo anesthesia, or wish to avoid mesh.

Some data suggest that objective and subjective success rates are lower with bulking agent treatment compared with the gold standard MUS procedure. However, in the appropriately selected patient, urethral bulking agents may be considered primary treatment due to their associated low morbidity and, as recently reported with newer nonparticulate agents, high subjective success rates. If the patient is not satisfied with the results of bulking treatment, surgical repair with any type of sling remains a subsequent option. This feature adds to the potential viability and appropriateness of considering a bulking agent as a primary treatment. ●

FAST TRACK

In the appropriately selected patient, urethral bulking agents may be considered primary treatment due to their associated low morbidity and, as recently reported with newer nonparticulate agents, high subjective success rates

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ILLUSTRATION: VELERI/SHUTTERTOCK

ROUNDTABLE

Work-life balance: How 5 surgeons manage life in and out of the operating room

Balancing work, home, and family is an acquired skill. Here, your colleagues offer their best advice based on their own trials and triumphs.

Expert panel featuring Patrick J. Culligan, MD; Kristie Greene, MD; Sally Huber, MD; Catherine Matthews, MD; and Charles Rardin, MD

Patrick J. Culligan, MD: We all know that burnout is an important problem among surgeons. In fact, it seems that, in the United States, we are working longer hours than ever before, and that higher education correlates with less balance in life. This dysfunction seems to start in school, when we are encouraged to be competitive, and overwork just becomes another way to compete. It's very easy to get swept up in the traditional model of academic medicine, the engine of which is competition and overwork.

My impression of our younger colleagues, however, is that many of them are not attracted to the traditional ivory tower research model of academic advancement to which many in previous generations aspired. They seem more concerned with work-life balance as their measure of success rather than the classic metrics of money and prestige. Everyone still needs role models and mentors, though, and that's where all of you come in. I asked each of you to be on this panel because I admire you for your varying approaches to work-life balance while achieving success as gynecologic surgeons. I thought others in the field might be inspired by hearing your stories.

Cultivating your passions

Kristie Greene, MD: What I have come to learn and appreciate is a really simple point: you do not have to do everything. Determining who you want to be both personally and professionally is step 1.

Granted, answering the question, "Who do I want to be?" is not as simple as it sounds. Many factors figure into the decisions we make in our personal and professional lives. Also, it is not a question we often stop and ask ourselves. From early on, we are placed on an escalator moving up through medical school, residency, fellowship, good job, better job, etc. We are so accustomed to being competitive, to winning, and to wanting to be the best that we sometimes forget to ask ourselves, "What is it exactly that I want, and why? What is my endpoint? And does it make me happy?"

Multitasking is regarded as a talent. As much as we would like to believe that we can do everything at the same time and do it all well, we actually can't. A friend of mine made me read a book a couple of years ago, called *Feeling Good*, by David Burns. The book encourages you to consider the different tasks you do in a day and rate how good you are at each of them on a scale of 1 to 10. It then asks you to think about how much enjoyment you derive from each of the tasks and about why you are doing the ones that bring you little to no enjoyment.

I ultimately decided that, for me professionally, the most important thing was my interest in global health. So I decided to do whatever it took to make this happen. But you don't get something for nothing, and everything comes with sacrifices.

Charles Rardin, MD: How exactly did you decide that you were going to focus your career toward pursuing international health? How did you *know* it was more important? And how did you overcome some of those obstacles?

Dr. Greene: You have to ask the hard question again about what brings you the most joy professionally and personally. That was the easy part of it for me because global health has always been that source of happiness and fulfillment for me. The more challenging parts are the sacrifices and hard choices that come with it. With global health, it can be difficult to balance the demands of a clinical practice.

All of our jobs are a business. I am still struggling with the money part of it. For my husband and I, that meant we had to start small—do what we could afford. But then it blossomed into something that was involving residents, fellows, and med students, which requires far more funding than we had. So I reached out to family. Most of our families donate to different organizations or charities every year, so why not donate to a loved one for something they are passionate about?

At the University of South Florida (USF), we set up a fund, a foundation for global health, which helps support our work abroad as well as the costs associated with involvement of our trainees. Right now, what we have is still small potatoes to a country, but we are making it happen by starting at a small level and growing it.

Beyond the money aspect, traveling abroad means less involvement in meetings, missed opportunities to teach courses that might interest me, and time away from my family. I guess my advice on this whole thing is that you can make things happen if they are important enough to you, and if you are willing to make sacrifices in other areas because you can't have it all.

Making time for you

Dr. Culligan: So you have found what is important to you, and you have found a way to make it happen. But you are faced with more work; you have given yourself additional work on top of your regular work. How do you make time for a personal life?

Catherine Matthews, MD: In preparing for this discussion, I decided to break down my advice into 3 buckets: The first bucket is discovering and knowing your authentic self. The second is building a community, which I'll elaborate on. And the third, which we have discussed, is to let go of the money.

Dr. Culligan: I love the concept of the authentic self, but how does that jive with a tendency to strive for perfection? We all think we can do it all. How do we narrow down to what really matters?

Dr. Matthews: We often focus on the things that bring us happiness and what we are good at, but it's the things that make us unhappy that tend to bring us down. It's the presence of unhappiness, not the absence of happiness, that seems to be the undoing of many, including myself.

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None of us are born with dramatic insight. It is experience that leads to insight. People who are actually present are able to gain insight through observation. A person becomes a better surgeon by observing the outcome of doing a stitch this way versus that; you learn how to do it by seeing what it looks like afterward.

Finding our authentic selves happens in much the same way. Having the presence of mind to ask the right questions, such as, "How am I feeling while I'm doing this?" leads to insights into the true self.

It takes a village

Dr. Greene: Catherine mentioned community earlier, and that is extremely important. The people who surround us can have a huge impact on the way we perceive things, including ourselves. Having a mix of people in our lives—some who practice medicine and others who don't—helps us stay balanced and answer some of the tough questions. Catherine, for example, has helped me in various stages of my career to ask myself meaningful questions and get real answers.

Dr. Rardin: Part of finding balance is luck, and part of it is making a choice between money and everything else. In considering my first job out of training, I knew that money had the potential to distract me from what was important to me. So I chose a position that was almost entirely salaried so that the decisions I made clinically, surgically, and regarding work-life balance would be less likely to directly impact what was important to me.

Sally Huber, MD: I am still in the "getting there" phase of my life, but one thing I have found is that getting my family involved and excited about what I do has made them much more accepting of when I have longer work days or work to do on the weekend. My spouse has become quite involved with what I have been doing with transgender health in Atlanta. It has been a great bonding experience; she shares my passions, and together we are creating something about which we both can be proud.

When work invades home life

Dr. Culligan: That is great. Sally, I think when we talked, you were just learning about the necessity of mental separation and of not taking your work home with you, which is so hard for all of us with all of our devices.

Dr. Huber: Yes, this year has been about seeing what works best as far as being efficient at work and having quality time at home. At the end of every day I ask myself, "What worked well today? What didn't work well? What else can I do to maximize time with my family?" I am slowly becoming more efficient, but it has been a challenge. During fellowship, your day is pretty set, but once you are practicing on your own, your hours and responsibilities are completely different, and you have to figure out what works best for you, your values, and your expectations of private life. It takes some time, and I am still figuring it out.

Dr. Culligan: How often would you say that you bring work home? I try hard once I am home to quit working, but sometimes on the weekends I break that rule.

Dr. Matthews: I must say that I do feel like there are certain times when I am better at that than others. Work comes in waves with pressing deadlines. If I averaged it out, probably a third of the time I have some email or some conference call or something that I have got to do at home. I do really try to limit the obligations that I have after 5:30 or 6:00 pm. I resent intrusions after that time. As far as weekends, I delegate about one weekend every 2 months to work, instead of doing a little bit every weekend.

Dr. Greene: I agree. I try hard to make 5:30 to 7:30 pm unequivocal time for a family dinner and time for my kids. During that time, I do not have my phone near me so I can't look at email or texts. I try not to schedule conference calls. I try to be there to read books to my kids at night. Then if I need to do work, I do it later at night, which interferes with time with my spouse, and is not ideal, but that's what happens.

Dr. Matthews: One of the things that I think is a huge part of work-life balance is work-related travel. When you are present at work on a consistent basis, the work does not pile up to the extent that it does when you are absent on a trip. When you come back, you invariably pay the price by seeing more patients and doing more surgery. Then it becomes a stressful event.

My advice to young people is to be very thoughtful about planning trips, especially distant ones. You do not want to sit on a plane all day

when you could be doing something more productive. If I could have done something differently in my mid-career, I would have traveled less.

Prioritizing "out of office" time

Dr. Greene: How do you all mentally separate yourself from work, so that when you are on vacation with your family you are not thinking about the office, the patients, and all of the things on your to-do list?

Dr. Rardin: I don't have a great answer for that except that it is about being present. You have to decide that now is the time when I am home, now is the time when I am a parent, now is the time when I am a boy scout leader, etc. I guess maybe it's a skill, or maybe it's about making something a priority. Work will always be waiting for you when you turn your attention back to it.

Dr. Matthews: Kristie, the answer to your question goes back to community. Partners in a practice cover for each other. You have to trust them to take care of things so that you can relax during your time away.

Some people recommend not scheduling challenging cases right before going away because invariably something goes wrong, and then you are asking, "Why did I schedule 3 colpopexies before getting on a plane?"

Dr. Rardin: Yes, I completely agree with all of that. Personally, I feel fortunate that I can compartmentalize pretty well. When I am home with my kids, I allow myself to shed some of the doctor/surgeon/leadership persona; I am able to be goofy and completely non–doctor-like. It works to help me leave work behind.

Dr. Matthews: Other things you can do include setting up an out-of-office notice on your email that says when you will be back and what to do in case of urgent matters. This basically says to the world, "Don't expect to hear from me until X date." It removes the expectation that you will respond sooner. Otherwise, we would all be on our smartphones all the time and not enjoying our time away.

What I wish I knew then

Dr. Culligan: How would you complete the sentence, "I wish they had told me X when I was embarking on my career?"

Dr. Rardin: I keep coming back to the phrase, "Don't do anything that you can reasonably pay someone else to do." By that I mean, if you don't get energy from housework, consider spending some of your money to get help with the housework. Resolve to make a relatively small expenditure to maximize the quality of the time that you give to yourself and your family. Those are the sorts of things that I think can go a long way.

Dr. Culligan: Charley, your wife is an ObGyn. How do you navigate a dual medical career household? What advice do you have for others?

Dr. Rardin: When I was going into fellowship, we had a conversation about how hard it is for both people in a relationship to have an academic fire in the belly and to be truly engaged in climbing the academic ladder. We made a decision that Jane would go into private practice. There has got to be some give and take in a dual medical relationship; a lot of sacrifices and compromises need to happen. We are fortunate in that there are complementary aspects to our jobs. We both spend about the same number of nights away from the house, but my travel is more in chunks and hers is overnight calls for labor and delivery. We have different ways of (briefly) single-parenting, and you have to come up with ways to handle the domestic chores.

Dr. Matthews: I wish someone had explained to me that the people you work with are much more important than the place. The human connection is what defines your experience, much more than any ego-driven outcome.

Dr. Greene: I wish someone had explained to me the competing aspects of academic medicine. The cards are stacked in a way that make it difficult for you to win. For example, you may love to teach and may be really good at it, but if you let your students handle too many cases, your relative value units plummet and then the hospital is on your back. There are the interests of people, and there are the interests of the business. Everything is a balance, and it's really tricky.

Dr. Huber: Luckily, Pat counselled me as I was finishing my fellowship about the importance of negotiating a good contract, of being pushy and knowing what you want out of it and knowing what your limitations are. I joined a private practice that had 3 different physical locations. If I had to drive to all of them, as they wanted, it would have meant up to a one-and-a-half-hour commute. But

I pushed to stay in one location and to put that extra hour to better use. I am glad I did, but it was terrifying at the time because I didn't want to lose the offer. I know people that did not do that and took the first thing they got. Now, they are driving all over the place or they have these crazy hours or terrible call responsibilities that if they had just been a little firmer, they probably could have gotten out of. As they start trying to find work-life balance, they are already handicapped.

Passions outside the office

Dr. Culligan: One thing I would like to touch on is what is going on in each of your personal lives because all of you have interesting stories to tell outside of what you do professionally. What drives you other than medicine?

Dr. Rardin: I am the father of 3 boys. The oldest one just got his Eagle Scout rank yesterday in Boy Scouts. I would be a woodworker if I wasn't in medicine. I am a Deacon at church. And I love to spend my downtime reading with my family in front of the fireplace.

Dr. Matthews: For me, it's music. When my husband and I first met, he asked me if I played a musical instrument. I said I played the cello in primary school. He said, "Great, go rent a cello." I was never at all interested in playing the cello by myself, but because he plays guitar and piano we became able to play a lot of music together. Our son, Alexander, plays drums. We now have a family band.

In addition, I do yoga. I would never have labeled myself an anxious person, but I learned through this process that I am and need to manage it. It took a lot of years to figure that out. If I don't leave myself an hour each day to go to a yoga class, I am not a happy person and neither is anyone around me. Also, I get tremendous pleasure from reading books and magazines as opposed to watching a screen.

Dr. Greene: I have found that my passions outside of work often change depending on my stage of life. Right now, I have two young babies and so my life outside of work revolves around them. Before the babies, my dad, who lives in Buffalo, was ill. So for awhile, we were flying to Buffalo almost every weekend that I was not on call. I would say, in general what fuels me is connecting with the people I love as often as I can. A typical night involves me and my husband going for a walk with our kids and dog after dinner and talking to each other. We connect with neighbors and chat on the front porch. It doesn't really matter what we are doing; it is about being surrounded by people who matter.

Dr. Huber: It's similar for me. Having a child completely shifts your world view. My goal every day is to give my daughter her first feeding in the morning and to get home as soon as possible at the end of the day to do her last feeding and put her to sleep. She crawled for the first time yesterday, and I was so excited that I could be there for that.

Also, I love being outdoors. I love hiking and camping. Going on a hike and being outside with nature is my way of decompressing.

Thinking about upcoming generations

Dr. Matthews: One other thing I would like to propose is looking at what can we do to make the profession better for the next generation. As a group, our profession is somewhat inflexible. We tend to fall into the trap of, "since this is the way we have always done it this is how we should continue doing it." The OR still starts at 7:00 or 7:30 am, ignoring the need for school drop-offs, etc. We are not innovative about flexibility in the work week. Honestly, it does not work well for many people, patients and physicians alike. Flexible scheduling should be something that is on the table for both men and women who are trying to balance being full-time parents and full-time surgeons. We need to create an environment in which it is okay for you to spend 10 years instead of 6 as an assistant professor because you are also a young parent, and it will not count against you when you come up for promotion.

Dr. Culligan: I agree with you, Catherine. Full "Professor" is a nice title, but it means time away from family and a lot of other things. Each of us has to decide whether it is worth it, especially since it often does not come with any extra money.

Dr. Huber: A question on a recent survey of residents asked, "Do you see yourself going into private practice or academic medicine when you've completed your residency?" When I was a resident, everyone wanted to go into academic medicine, but now it seems like more and more residents have their sights

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Marci S.
Two-time breast cancer survivor
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set on private practice because that is where they see the opportunities to create work-life balance.

In the academic world, you have to try to get a promotion in X number of years, and get X number of publications, and be a great teacher, doctor, and administrator all at the same time. I am wondering if we are going to start seeing more and more residents and fellows going into private or hospital-owned practice where there aren't those added expectations.

Dr. Rardin: I agree, and we are back to what we said in the beginning about doing an honest assessment of what is meaningful and important. We are all trained to try to reach for that shiny brass ring, but do we really want that brass ring? Will it be an asset or a hindrance once we get it? It is okay to be honest and say, "I really don't want that promotion. I would rather spend more time with my family." ■

BRINGING YOUR IDEAS TO MARKET

The professional advancement of drug and device innovation

This entrepreneur offers his past paths to success, as well as bumps to avoid, while taking a product or drug development from an idea to standard of care

Marc Beer

I often say that there are both "guardrail" days and very good days when it comes to the ins and outs of health care builds and product launches. The process is much like starting down the path of a country road in the middle of a blizzard—unless you have dependable wipers and a good defrost system, that path can get murky very quickly. With this article I hope to offer my counsel to inventors, featuring a few of my prior launches as well as case studies of health care launches I was not involved with, and sharing the lessons learned and hurdles that were overcome. I encourage all entrepreneurs to act on their ideas because, in the world of health care startups, the only failure is not acting on an invention.

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Case study 1: Cerezyme

Today, Cerezyme is indicated for patients with Gaucher, which is a lysosomal storage disorder. Cerezyme's first-generation product, called Ceredase, was a human tissue-derived protein that we extracted from human placentas. At the time, the concept of moving this program forward was denied by the Board of Directors because they said that even if you could collect enough placentas to make the enzyme, it would be too expensive to manufacture. In fact, early scale-up modeling for manufacturing the protein demonstrated that Genzyme would need 4 tons of placentas per Gaucher patient per year.

Gaucher is a severe, early-onset disease that has a significant negative outcome for patients. Patients with Gaucher are in dire need of treatment. Genzyme went forward with the Ceredase program by financing it through the families of patients with the disease, by starting an LLC separate from the business and funding the initial clinical trial and the development of the protein through the families of Gaucher patients. That approach was a successful endeavor. A great example of a creative capital structure to advance a program.

This was in the late 1980s/early 1990s, and at the height of the AIDS challenge. Genzyme based the manufacturing in Lille, France, and we cryopreserved placentas in the United States and Europe and shipped them to Lille to be processed into therapy. Genzyme eventually received approval for Ceredase from the US Food and Drug Administration (FDA) and the European Medicines Agency. At the height of the placenta collection, we were gathering about 10% to 15% of the

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placentas in the United States and 30% to 40% of the placentas in Europe. Resources supply became an issue until we developed a recombinant form of the protein, accomplished by using a manufacturing system called a CHO cell line.

This is a very good success story: If this invention was not pursued, Gaucher patients would not benefit from the treatment today. In addition, there are a plethora of patients with different lysosomal storage disorders treated with additional proteins that have been aided by us going through the entire development, manufacturing, and global commercialization process. We figured out how to manufacture and deliver the treatment, working through multiple countries' political systems, and today the therapy is paid for by insurance and government systems on a worldwide basis.

Case study 2: ThinPrep

I like to use the approval of ThinPrep as an example of avoiding a false negative—a stoppage in the development of the product or drug for the wrong reasons. False negatives, in my mind, occur when you are developing a technology and you run into issues during the clinical phase and/or with FDA approval, or with a technical failure or you run out of capital prior to knowing whether or not the innovation actually works. In the case of ThinPrep, a poorly run clinical trial almost resulted in a false negative.

The company at the time was Cytyc, and an initial clinical study presented to the FDA yielded a neutral-negative outcome. The FDA said that there were not enough data to show the differentiation from the current Pap smear standard of care.

The founders of the company at that time had inherited the study protocol from a prior leadership team, so they had to finish the trial with the initial protocol. Given the FDA's advisement, they developed a new trial. It took the persistence of these two founders, who mortgaged their homes and spent their personal dollars to take this through the next wave of clinical development. In the end it was successful. The revised clinical trial yielded an approval for ThinPrep, which is now considered a standard of care.

The use of ThinPrep reduced cervical cancer deaths by 40% from preapproval. The challenging path from clinical development to eventual commercial launch and physician leadership in advancing patient care makes the story of ThinPrep a great example of not allowing an early false negative of a poorly designed and run clinical trial stop important innovation.

Case study 3: Cologuard

The development of Cologuard is a case study demonstrating that, sometimes, when your first attempt does not work, you need to have the persistence to raise additional capital and/or use a slightly different technical approach. The approval story of Cologuard is important to share because it is an important cancer screening diagnostic, using DNA from stool samples to test for colon cancer, giving access to important colon cancer screening to many patients. Currently, caregivers are only scraping the surface with Cologuard's ability to screen the population. There are many more patients that need access to the test, and I believe they will get it in the years ahead.

Cologuard went through a first- and second-generational technical failure. They could not get the test's specificity and sensitivity to be at the level of a screening tool; there were too many false-positive results. With the third iteration came the technical breakthrough, and a very large, expensive study was conducted—one the leadership team was criticized for. However, that study yielded the data that achieved a *New England Journal of Medicine* article, and reimbursement support across the country. The combination of the right technical team and the right leadership team, who planned a proper commercial launch, with a CEO that supported the extensive clinical study, has resulted in the fourth generation of Cologuard—an important breakthrough offering a very useful new standard of care in colon cancer detection and screening.

Pearls for moving your innovations forward

Because of my experience in undergoing health care start-ups, and contributing to several of those advancements of innovation, many inventors approach me for advice on their paths from idea to full-concept company. Here are a few of my lessons learned.

Consider purpose, not financial gain, first and foremost. Financial gain is typically the by-product or outcome of a standard-of-care breakthrough for inventors, but it's a very hard road. Pursue your invention for advancing patient care and moving a new standard of care forward in health care versus financial gain at the end.

Determine whether your invention is a product or a company, or potentially, not capitalizable at all. Figure this out early. Analyze your idea to make sure it is sound and truly novel. Analyze the competition and to make sure it is sound and truly novel. Analyze the competition and the market dynamics to support a new product. Can the development path be defined very clearly to raise capital? Is your innovation a big enough breakthrough in the market with several current products to actually make a difference in patient outcomes (and eventually achieve product reimbursement)? The creation of a company may be the right strategy if the innovation can support a differentiated enough breakthrough where you can actually support all the infrastructure to build the business. If you find that the market is not there to support and develop your idea to eventual success, backing off early is important to preserve invested capital.

Protect early. Is your invention patentable, or has someone else already thought of the idea? What kind of patent(s) are appropriate? Where, geographically, do you want to protect your invention? Find a good patent attorney in your local area, early in the process, to help you answer all of these critical questions. Patents are expensive to file and maintain, but it is not expensive to do a literature search to find out if your idea is novel. A provisional patent, which would be your first step, is an important cost-effective step.

Capital is out there. If your invention or idea deserves capital, it is available. I will address raising capital in more detail in the next section.

Consider regulatory and manufacturing as achievable hurdles. Inventors often get tripped up here, considering the regulatory hurdles and manufacturing too challenging and abandoning their ideas because the risk is too great. Regulatory and manufacturing are very important aspects of health care standard-of-care builds. Cutting corners is not an option. That said, regulatory and manufacturing should not stop you. Challenges often can be worked through as long as the clinical need is there, and the clinical data support bringing that technology forward.

Consider corporate partnerships. I am a fan of corporate partners. But which ones should you target, and when and why? Corporate partnerships can bring significant capital, which is great, but there is enough investor capital out there that you should not pursue a corporate partner just for capital. The main benefit of a corporate partner is enterprise intellect. They typically know more about the field that you are entering than the investors or a small company leadership team.

Establish and listen to advisors. When thinking about who to trust, research their track record. Advisors who have gone through this process before, and specifically in your product area, are important to have access to.

Persistence is key. I have observed a tremendous "compression of innovation" in the health care areas that I have been involved with—human tissue-derived proteins, robotic surgery, stem cell therapy, and digital health (which is still in its infancy). For each of these breakthrough categories, early on, it appeared that it couldn't be done. However, after the first 2 or 3 major breakthroughs in each one of these areas, a compression of innovation occurred. For instance, after approximately 15 years of protein development, we came out with the recombinant manufacturing systems for proteins. Very quickly, within 10 years, there were more than 70 proteins on the market. The persistence of the inventors to overcome early obstacles in each of these health care areas was critical to future success in each area.

Raising capital

There are different investors who specialize in different types of investment opportunities. The first phase of raising capital is the seed round—where there is typically early data, or even no data and just a concept. From this seed round forward, there is less risk as you develop your technology; thus, there are different investors that support different stages of development and that specialize in different types of investing. It is important to target the right investors and raise enough capital to be able to go achieve multiple operational milestones.

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Otherwise, when you go through your first round of capital, or the Series A or B financing rounds, there may not be a set of investors out there to fund the company moving forward. Health care investors will make it known that they invest in certain rounds of capital. You can determine who those investors are by doing a search online.

A mistake health care inventors can make is not taking enough capital from investors, because they are concerned about dilution. I advise investors not to focus on dilution but rather on, how big can you make "the pie" (value of the company) worth? The entire process is about bringing a true product through to a new standard-of-care curve.

Trust is the most important thing to earn with investors, and there is zero tolerance for a lack of trust. Share your vision as the inventor with investors, who want to know where this category could be in the next 5 or 10 years. Clinical data will always win, and health care investors and industry leaders should be focused on executing the most robust clinical data to demonstrate the clearest potential clinical outcome. Investors will follow a good plan that has been developed to achieve FDA approval, successful commercialization or "go to market" launch, and eventual reimbursement to support a true standard-of-care change.

Failure is defined by inaction

The 3 case studies that I have shared were success stories because the ideas and inventions were acted upon. When I was at Genzyme, we built the company up to more than $1 billion in revenue. We commercialized proteins in over 50 countries. Most importantly, many patients benefited from the innovation. If you have an invention and an idea, act on it—and surround yourself with great people in every discipline. Having the right people and team is extremely important. ■

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Laparoscopic specimen retrieval bags in gyn surgery: Expert guidance on selection

For MIGS procedures, understanding the features of specimen retrieval systems (which vary widely), as well as the pathology's characteristics, is essential to surgical decision making

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IN THIS ARTICLE

The use of minimally invasive gynecologic surgery (MIGS) has grown rapidly over the past 20 years. MIGS, which includes vaginal hysterectomy and laparoscopic hysterectomy, is safe and has fewer complications and a more rapid recovery period than open abdominal surgery.[1,2] In 2005, the role of MIGS was expanded further when the US Food and Drug Administration (FDA) approved robot-assisted surgery for the performance of gynecologic procedures.[3] As knowledge and experience in the safe performance of MIGS progresses, the rates for MIGS procedures have skyrocketed and continue to grow. Between 2007 and 2010, laparoscopic hysterectomy rates rose from 23.5% to 30.5%, while robot-assisted laparoscopic hysterectomy rates increased from 0.5% to 9.5%, representing 40% of all hysterectomies.[4] Due to the benefits of minimally invasive surgery over open abdominal surgery, patient and physician preference for minimally invasive procedures has grown significantly in popularity.[1,5]

Because incisions are small in minimally invasive surgery, surgeons have been challenged with removing large specimens through incisions that are much smaller than the presenting pathology. One approach is to use a specimen retrieval bag for specimen extraction. Once the dissection is completed, the specimen is placed within the retrieval bag for removal, thus minimizing exposure of the specimen and its contents to the abdominopelvic cavity and incision.

The use of specimen retrieval devices has been advocated to prevent infection, avoid spillage into the peritoneal cavity, and minimize the risk of port-site metastases in cases of potentially cancerous specimens. Devices include affordable and readily available products, such as nonpowdered gloves, and commercially produced bags.[6]

While the use of specimen containment systems for tissue extraction has been well described in gynecology, the available systems vary widely in construction, size, durability, and shape, potentially leading to confusion

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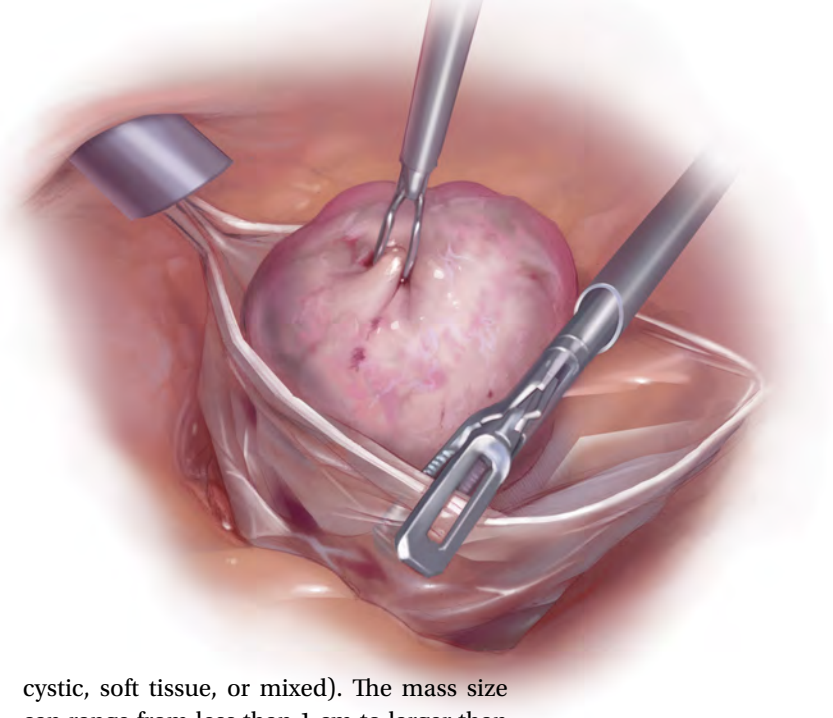
and suboptimal bag selection during surgery.[7] In this article, we review the most common laparoscopic bags available in the United States, provide an overview of bag characteristics, offer practice guidelines for bag selection, and review bag terminology to highlight important concepts for bag selection.



Controversy spurs change

In April 2014, the FDA warned against the use of power morcellation for specimen removal during minimally invasive surgery, citing a prevalence of 1 in 352 unsuspected uterine sarcomas and 1 in 498 unsuspected uterine leiomyosarcomas among women undergoing hysterectomy or myomectomy for presumed benign leiomyoma.[8] Since then, the risk of occult uterine sarcomas, including leiomyosarcoma, in women undergoing surgery for benign gynecologic indications has been determined to be much lower.

Nonetheless, the clinical importance of contained specimen removal was clearly highlighted and the role of specimen retrieval bags soared to the forefront. Open power morcellation is no longer commonly practiced, and national societies such as the American Association of Gynecologic Laparoscopists (AAGL), the Society of Gynecologic Oncology (SGO), and the American College of Obstetricians and Gynecologists (ACOG) recommend that containment systems be used for safer specimen retrieval during gynecologic surgery.[9-11] After the specimen is placed inside the containment system (typically a specimen bag), the surgeon may deliver the bag through a vaginal colpotomy or through a slightly extended laparoscopic incision to remove bulky specimens using cold-cutting extraction techniques.[12-15]

Know the pathology's characteristics

In most cases, based on imaging studies and physical examination, surgeons have a good idea of what to expect before proceeding with surgery. The 2 most common characteristics used for surgical planning are the specimen size (dimensions) and the tissue type (solid, cystic, soft tissue, or mixed). The mass size can range from less than 1 cm to larger than a 20-week sized fibroid uterus. Assessing the specimen in 3 dimensions is important. Tissue type also is a consideration, as soft and squishy masses, such as ovarian cysts, are easier to deflate and manipulate within the bag compared with solid or calcified tumors, such as a large fibroid uterus or a large dermoid with solid components.

Specimen shape also is a critical determinant for bag selection. Most specimen retrieval bags are tapered to varying degrees, and some have an irregular shape. Long tubular structures, such as fallopian tubes that are composed of soft tissue, fit easily into most bags regardless of bag shape or extent of bag taper, whereas the round shape of a bulky myoma may render certain bags ineffective even if the bag's entrance accommodates the greatest diameter of the myoma. Often, a round mass will not fully fit into a bag because there is a poor fit between the mass's shape and the bag's shape and taper. (We discuss the concept of a poor "fit" below.) Knowing the pathology before starting a procedure can help optimize bag selection, streamline operative flow, and reduce waste.

Overview of laparoscopic bag characteristics and clinical applications

The **TABLE** (pages 38–39) lists the most common laparoscopic bags available for purchase in the United States. Details include the trocar size, manufacturer, product name, mouth

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TABLE Features of common laparoscopic retrieval bags available in the United States

Trocar size	Product name (manufacturer)	Mouth diameter, width X length, cm	Bag height, cm	Volume, mL	Bag taper	Material	Clinical application	Bag shape
5 mm	TissueBag Premium 5mm (A.M.I.)	4.6 X 6.0	17.0	100	Minimal taper	Polyurethane	Salpingectomy	
8 mm	Anchor TRS-ROBO-8 (ConMed)	4.0 X 6.6	14.0	125	Gradual taper	Ripstop nylon	Small fibroid, solid adnexal mass	
	Inzii 5[a] (Applied Medical)	4.4 X 8.0	19.0	180	Gradual taper	Polyurethane	Salpingectomy	
10 mm	TissueBag Premium 10mm (A.M.I.)	6.0 X 8.0	18.5	210	Gradual taper	Polyurethane	Oophorectomy, simple cysts	
	Endo Catch Gold (Covidien/ Medtronic)	6.3 X 7.1	15.0	220	Gradual taper	Polyurethane	Oophorectomy, simple cysts	
	Endopouch Retriever (Ethicon)	5.4 X 5.8	15.0	224	Gradual taper	Polyurethane	Oophorectomy, simple cysts	 ©Ethicon, Inc.
	Inzii 10 (Applied Medical)	5.2 X 7.8	11.5	225	Gradual taper	Polyurethane	Oophorectomy, simple cysts	
	Anchor TRS100SB2 (ConMed)	4.9 X 8.1	14.0	235	Gradual taper	Ripstop nylon	Dermoids, fibroids	
	ReliaCatch 10 mm (Covidien/ Medtronic)	6.4 X 7.7	16.6	275	Gradual taper	Ripstop nylon	Dermoids, fibroids	

TABLE Features of common laparoscopic retrieval bags available in the United States *(continued)*

Trocar size	Product name (manufacturer)	Mouth diameter, width X length, cm	Bag height, cm	Volume, mL	Bag taper	Material	Clinical application	Bag shape
12 mm	Anchor TRS-ROBO-12 (ConMed)	6.7 X 7.6	14.0	300	Steep taper	Ripstop nylon	Dermoids, fibroids	
15 mm	Endo Catch II (Covidien/ Medtronic)	12.7 X 9.7	23.6	1,500	Gradual taper	Polyurethane	Large cystic masses	
	Anchor TRS-VATS-15 (ConMed)	7.0 X 17.0	25.4	1,550	Steep taper	Ripstop nylon	Fibroid uteri	
	Anchor TRS175SB2 (ConMed)	10.2 X 16.0	25.4	1,550	Gradual taper	Ripstop nylon	Fibroid uteri	
	Inzii 12[b] (Applied Medical)	9.7 X 13.0	23.6	1,600	Gradual taper	Polyurethane	Large simple cysts	
	Anchor TRS190SB2 (ConMed)	11.3 X 16.5	26.5	1,850	Steep taper	Ripstop nylon	Fibroid uteri	
25 mm	Alexis Contained Extraction System (Applied Medical)	14 X 14.0	28.5	3,400	No taper	Polypropylene	Fibroid uteri, large cysts	
	Anchor TRS-TV-25 (ConMed)	13.5 X 16.5	38.1	4,000	No taper	Ripstop nylon	Fibroid uteri, large cysts	
	Alexis Contained Extraction System (Applied Medical)	17 X 17.0	37.0	6,500	No taper	Polypropylene	Fibroid uteri, large cysts	

[a]The Inzii 5-mm laparoscopic bag fits into the 5-mm Applied Medical Kii Access System trocar, which has a larger internal and outer diameter than a conventional 5-mm trocar. As such, this bag can also be inserted through a conventional 8-mm trocar, or requires removal of the 5-mm trocar prior to insertion of the bag directly through a 5-mm skin incision.

[b]The Inzii 12-mm laparoscopic bag fits into the 12-mm Applied Medical Kii Access System trocar, which has a larger internal and outer diameter than a conventional 12-mm trocar. As such, this bag can also be inserted through a conventional 15-mm trocar, or requires removal of the 12-mm trocar prior to insertion of the bag directly through a 12-mm skin incision.

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diameter, volume, bag shape, construction material, and best clinical application.

The following are terms used to refer to the components of a laparoscopic retrieval bag:

- Mouth diameter: diameter at the entrance of a fully opened bag (**FIGURE 1**)
- Bag volume: the total volume a bag can accommodate when completely full
- Bag rim: characteristics of the rim of the bag when opened (that is, rigid vs soft rim, complete vs partial rim mechanism to hold the bag open) (**FIGURE 2**)
- Bag shape: the shape of the bag when it is fully opened (square shaped vs cone shaped vs curved bag shape) (**FIGURE 2**)
- Bag taper (severity and type): extent the bag is tapered from the rim of the bag's entrance to the base of the bag; categorized by taper severity (minimal, gradual, or steep taper) and type (continuous taper or curved taper) (**FIGURE 3**)
- Ball fit: the maximum spherical specimen size that completely fits into a bag and allows it to cinch closed (**FIGURE 4**)
- Bag strength: durability of a bag when placed on tension during specimen extraction (weak, moderate, or extremely durable).

FIGURE 1 Laparoscopic retrieval device components and terminology

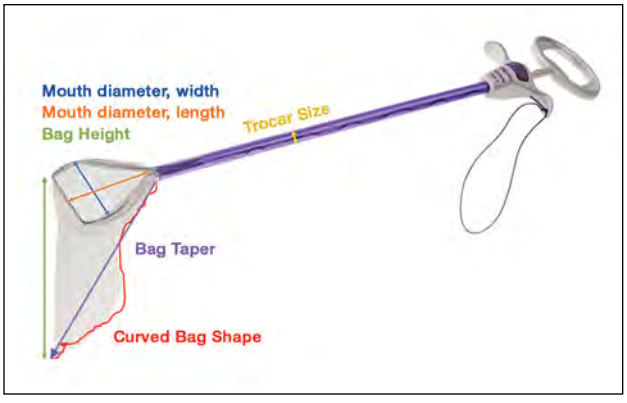


FIGURE 2 Shapes of laparoscopic retrieval bags

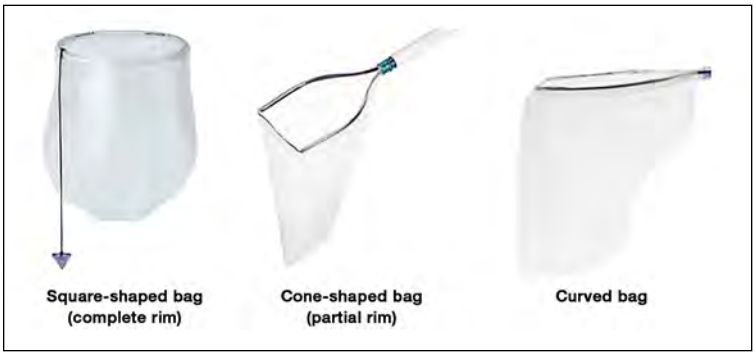


FIGURE 3 Taper configuration on laparoscopic retrieval bags

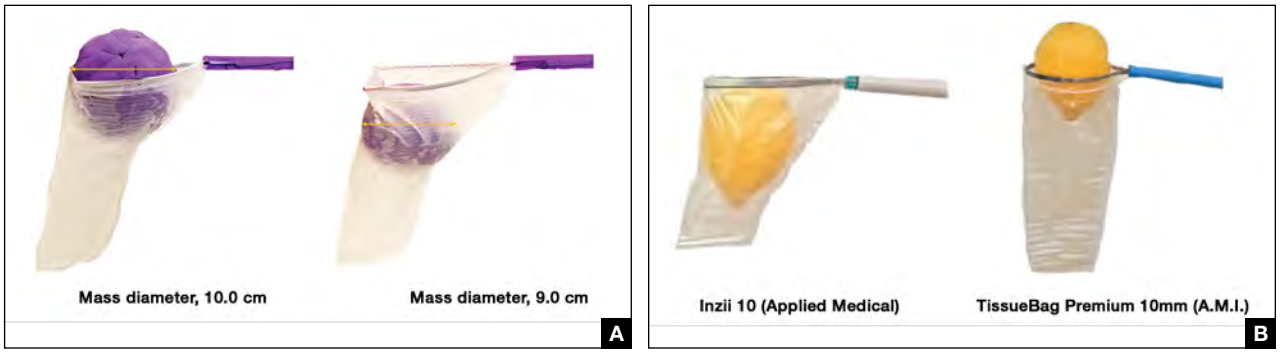
Mouth diameter

Bag manufacturers often differentiate bag sizes by indicating "volume" in milliliters. Bag volume, however, offers little clinical value to surgeons, as pelvic mass dimensions are usually measured in centimeters on imaging. Rather, an important characteristic for bag selection is the diameter of the rim of the bag when it is fully opened—the so-called bag mouth diameter. For a specimen to fit, the 2 dimensions of the specimen must be smaller than the dimensions of the bag entrance.

Notably, the number often linked to the specimen bag—as, for example, in the 10-mm Endo Catch bag (Covidien/Medtronic)—describes the width of the shaft of the bag before it is opened rather than the mouth diameter of the opened bag. The number actually correlates with the trocar size necessary for bag insertion rather than with the specimen size that can fit into the bag. Therefore, a 10-mm Endo Catch bag cannot fit a 10-cm mass, but rather requires a trocar size of 10 mm or greater for insertion of the bag. Fully opened, the mouth diameters of the 10-mm Endo Catch bag are roughly 6 cm x 7 cm, which allows for delivery of a 6-cm mass.

Because 2 bags that use the same trocar size for insertion may have vastly differing

FIGURE 4 Effects of laparoscopic retrieval bag taper and mouth diameter on ball fit



A Bag taper. Two examples of masses with different mass diameters within the same Anchor TRS175SB2 bag (ConMed). **Left:** The mass diameter of the specimen is just able to be accommodated by the mouth diameter of the bag, but the degree of bag taper hinders closure. The ball fit for the bag is smaller than the mouth diameters. **Right:** Although the specimen's mass diameter is smaller than the mouth diameter of the bag, the ball fit is appropriate, allowing for the bag to be cinched closed.
B Bag mouth diameter. Although these bags have the same trocar size, their mouth diameters are different, resulting in different ball fits. **Left:** The specimen fits nicely within the bag. **Right:** The specimen passes through the mouth diameter, but because of bag's taper it is unable to be placed within the bag.

bag dimensions, the surgeon must know the bag mouth diameters when selecting a bag to remove the presenting pathology. For example, the Inzii 12 (Applied Medical) laparoscopic bag has mouth diameters of 9.7 cm × 13.0 cm, whereas the Anchor TRS-ROBO-12 (ConMed) has mouth diameters of 6.7 cm × 7.6 cm (TABLE). Although both bags can be inserted through a 12-mm trocar, both bags cannot fit the same size mass for removal.

Shape and taper

Laparoscopic bags come in various shapes (curved, cone, or square shaped), with varying levels of bag taper (steep, gradual, or no taper) (FIGURES 2 and 3). While taper has little impact on long and skinny specimens, taper may hinder successful bagging of bulky or spherical specimens.

Each bag has different grades of taper regardless of mouth diameter or trocar size. For round masses, the steeper the taper, the smaller the mass that can comfortably fit within the bag. This concept is connected to the idea of "ball fit," explained below.

In addition, bag shape may affect what mass size can fit into the bag. An irregularly shaped curved bag or a bag with a steep taper may be well suited for removal of multiple specimens of varying sizes or soft masses that are malleable enough to conform to the bag's shape (such as a ruptured ovarian cyst). Alternatively, a square-shaped bag or a bag with minimal taper would better accommodate a round mass.

Ball fit

When thinking about large circular masses, such as myomas or ovarian cysts, one must consider the ball fit. This refers to the maximum spherical size of the specimen that fits completely within a bag while allowing the bag to cinch closed. Generally, this is an estimation that factors in the bag shape, extent of the bag taper, bag mouth diameter, and specimen shape and tissue type. At times, although a mass can fit through the bag's mouth diameter, a steep taper may prevent the mass from being fully bagged and limit closure of the bag (FIGURE 4).

Curved bags like the Anchor TRS-VATS-15 (ConMed), which have a very narrow bottom, are prone to a limited ball fit, and thus the bag mouth diameter will not correlate with the largest mass size that can be fitted within the bag. Therefore, if using a steeply tapered bag for removal of large round masses, do not rely on the bag's mouth

FAST TRACK

Ball fit refers to the maximum spherical size of the specimen that fits completely within a bag while allowing the bag to cinch closed

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diameter for bag selection. The surgeon must visualize the ball fit within the bag, taking into account the specimen size and shape, bag shape, and bag taper. In these scenarios, using the diameter of the midportion of the opened bag may better reflect the mass size that can fit into that bag.

Bag strength

Bag strength depends on the material used for bag construction. Most laparoscopic bags in the United States are made of 3 different materials: polyurethane, polypropylene, and ripstop nylon.

Polyurethane and polypropylene are synthetic plastic polymers; in bag form they are stretchy and, under extreme force, may tear. They are best used for bagging fluid-filled cysts or soft pliable masses that will not require extensive bag or tissue handling, such as extraction of large leiomyomas. Polyurethane and polypropylene bags are more susceptible to puncture with sharp laparoscopic instruments or scalpels, and care must be taken to avoid accidentally cutting the bag during tissue extraction.

Alternatively, bags made of ripstop nylon are favored for their bag strength. Ripstop nylon is a synthetic fabric that is woven together in a crosshatch pattern that makes it resistant to tearing and ripping. It was developed originally during World War II as a replacement for silk parachutes. Modern applications include its use in sails, kites, and high-quality camping equipment. This material has a favorable strength-to-weight ratio, and, in case of a tear, it is less prone to extension of the tear. For surgical applications, these bags are best used for bagging specimens that will require a lot of bag manipulation and tissue extraction. However, the ripstop fabric takes up more space in the incision than polyurethane or polypropylene, leaving the surgeon with less space for tissue extraction. Thus, as a tradeoff for bag strength, the surgeon may need to extend the incision a little, and a small self-retracting wound retractor may be necessary to allow visibility for safe tissue extraction when using a ripstop nylon bag compared with others.

FAST TRACK

Trocar size for bag selection refers to the minimum trocar diameter needed to insert the laparoscopic bag

Trocar selection is important

While considering bag selection, the surgeon also must consider trocar selection to allow for laparoscopic insertion of the bag. Trocar size for bag selection refers to the minimum trocar diameter needed to insert the laparoscopic bag. Most bags are designed to fit into a laparoscopic trocar or into the skin incision that previously housed the trocar. Trocar size does not directly correlate with bag mouth diameter; for example, a 10-mm laparoscopic bag that can be inserted through a 10- or 12-mm trocar size cannot fit a 10-cm mass (see the mouth diameter section above).

A tip to maximize operating room (OR) efficiency is to start off with a larger trocar, such as a 12-mm trocar, if it is known that a laparoscopic bag with a 12-mm trocar size will be used, rather than starting with a 5-mm trocar and upsizing the port site incision. This saves time and offers intraoperative flexibility, allowing for the use of larger instruments and quicker insufflation.

Furthermore, if the specimen has a solid component and tissue extraction is anticipated, consider starting off with a large trocar, one that is larger than the bag's trocar size since the incision likely will be extended. For example, even if a myoma will fit within a 10-mm laparoscopic bag made of ripstop nylon, using a 15-mm trocar rather than a 10-mm trocar may be considered since the skin and fascial incisions will need to be extended to allow for cold-cut tissue extraction. Starting with the larger 15-mm trocar may offer surgical advantages, such as direct needle delivery of larger needles for myometrial closure after myomectomy or direct removal of smaller myomas through the trocar to avoid bagging multiple specimens.

Putting it all together

To optimize efficiency in the OR for specimen removal, we recommend streamlining OR flow and reducing waste by first considering the specimen size, tissue type, bag shape, and trocar selection. Choose a bag by taking into account the bag mouth diameter and the amount of taper you will need to obtain an

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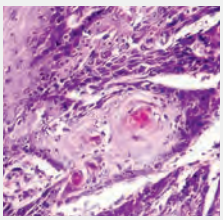

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appropriate ball fit. If the tissue type is soft and pliable, consider a polyurethane or polypropylene bag and the smallest bag size possible, even if it has a narrow bag shape and taper.

However, if the tissue type is solid, the shape is round, and the mass is large (requiring extensive tissue extraction for removal), consider a bag made of ripstop nylon and factor in the bag shape as well as the bag taper. Using a bag without a steep taper may allow a better fit.

After choosing a laparoscopic bag, select the appropriate trocars necessary for completion of the surgery. Consider starting off with a larger trocar rather than spending the time to upsize a trocar if you plan to use a large bag or intend to extend the trocar incision for a contained tissue extraction. These tips will help optimize efficiency, reduce equipment wastage, and prevent intra-abdominal spillage.

Keep in mind that all procedures, including specimen removal using containment systems, have inherent risks. For example, visualization of the mass within the bag and visualization of vital structures may be hindered by bulkiness of the bag or specimen. There is also a risk of bag compromise and leakage, whether through manipulation of the bag or puncture during specimen extraction. Lastly, even though removing a specimen within a containment system minimizes spillage and reports of in-bag cold-knife tissue extraction in women with histologically proven endometrial cancer have suggested that it is safe, laparoscopic bags have not been proven to prevent the dissemination of malignant tissue fragments.[16,17]

Overall, the inherent risks of specimen extraction during minimally invasive surgery are far outweighed by the well-established advantages of laparoscopic surgery, which carries lower risks of surgical complications such as bleeding and infection, shorter hospital stay, and quicker recovery time compared to laparotomy. There is no doubt minimally invasive surgery offers many benefits.

In summary, for best bag selection, it is equally important to know the characteristics of the pathology as it is to know the features of the specimen retrieval systems available at your institution. Understanding both the pathology and the equipment available will allow the surgeon to make the best surgical decisions for the case. ●

FAST TRACK

Consider starting off with a larger trocar rather than spending the time to upsize a trocar if you plan to use a large bag or intend to extend the trocar incision for a contained tissue extraction

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MRI's role in breast cancer screening for childhood cancer survivors

Nearly 16,000 children (up to age 19 years) face cancer-related treatment every year.[1] For girls and young women, undergoing chest radiotherapy puts them at higher risk for secondary breast cancer. In fact, they have a 30% chance of developing such cancer by age 50—a risk that is similar to women with a *BRCA1* mutation.[2] Therefore, current recommendations for breast cancer screening among those who have undergone childhood chest radiation (≥20 Gy) are to begin annual mammography, with adjunct magnetic resonance imaging (MRI), at age 25 years (or 8 years after chest radiotherapy).[3]

To determine the benefits and risks of these recommendations, as well as of similar strategies, Yeh and colleagues performed simulation modeling using data from the Childhood Cancer Survivor Study and two CISNET (Cancer Intervention and Surveillance Modeling Network) models.[4] For their study they targeted a cohort of female childhood cancer survivors having undergone chest radiotherapy and evaluated breast cancer screening with the following strategies:

- mammography plus MRI, starting at ages 25, 30, or 35 years and continuing to age 74
- MRI alone, starting at ages 25, 30, or 35 years and continuing to age 74.

They found that both strategies reduced the risk of breast cancer in the targeted cohort but that screening beginning at the earliest ages prevented most deaths. No screening at all was associated with a 10% to 11% lifetime risk of breast cancer, but mammography plus MRI beginning at age 25 reduced that risk by 56% to 71% depending on the model. Screening with MRI alone reduced mortality risk by 56% to 62%. When considering cost per quality-adjusted life-year gained, the researchers found that screening beginning at age 30 to be the most cost-effective.[4]

Yeh and colleagues addressed concerns with mammography and radiation. Although they said the associated amount of radiation exposure is small, the use of mammography in women younger than age 30 is controversial—and not recommended by the American Cancer Society or the National Comprehensive Cancer Network.[5,6]

Bottom line. Yeh and colleagues conclude that MRI screening, with or without mammography, beginning between the ages of 25 and 30 should be emphasized in screening guidelines. They note the importance of insurance coverage for MRI in those at risk for breast cancer due to childhood radiation exposure.[4]

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OBG MANAGEMENT

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clinicians and patients should be aware of data that support the continued use of levonorgestrel 52-mg IUS products for 6 years, and likely even longer. A low incidence of new significant events and a steady state of amenorrhea are also indications that users who like using a hormonal IUS will likely continue to do so for an extended time, if recommended. This extension, as well as continued study up to 10 years, will allow users who desire reversible long-acting hormonal contraception to have fewer removals and reinsertions; this in turn will decrease the risks and pain associated with IUS insertion and removal as well as health care costs.

Long-term IUS effectiveness

Overall, in users aged 16 to 35 years, 72% discontinued study participation, most frequently due to an adverse event (19.2%) or to seeking pregnancy (15.5%). Through 6 or more years of use, overall discontinuation rates for expulsion (4.0%) and bleeding symptoms (2.3%) were very low, with 2 expulsions occurring in year 6 and only 1 participant discontinuing in year 6 for a bleeding symptom. These findings are consistent with those found at 5 years of IUS use and are representative of continued efficacy as well as overall low frequency of new significant events with extended use.[11] ●

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