MDEDGE.COM/OBGYN | VOL 31, NO 2 | FEBRUARY 2019

OBG MANAGEMENT

A member of the MDedge Network

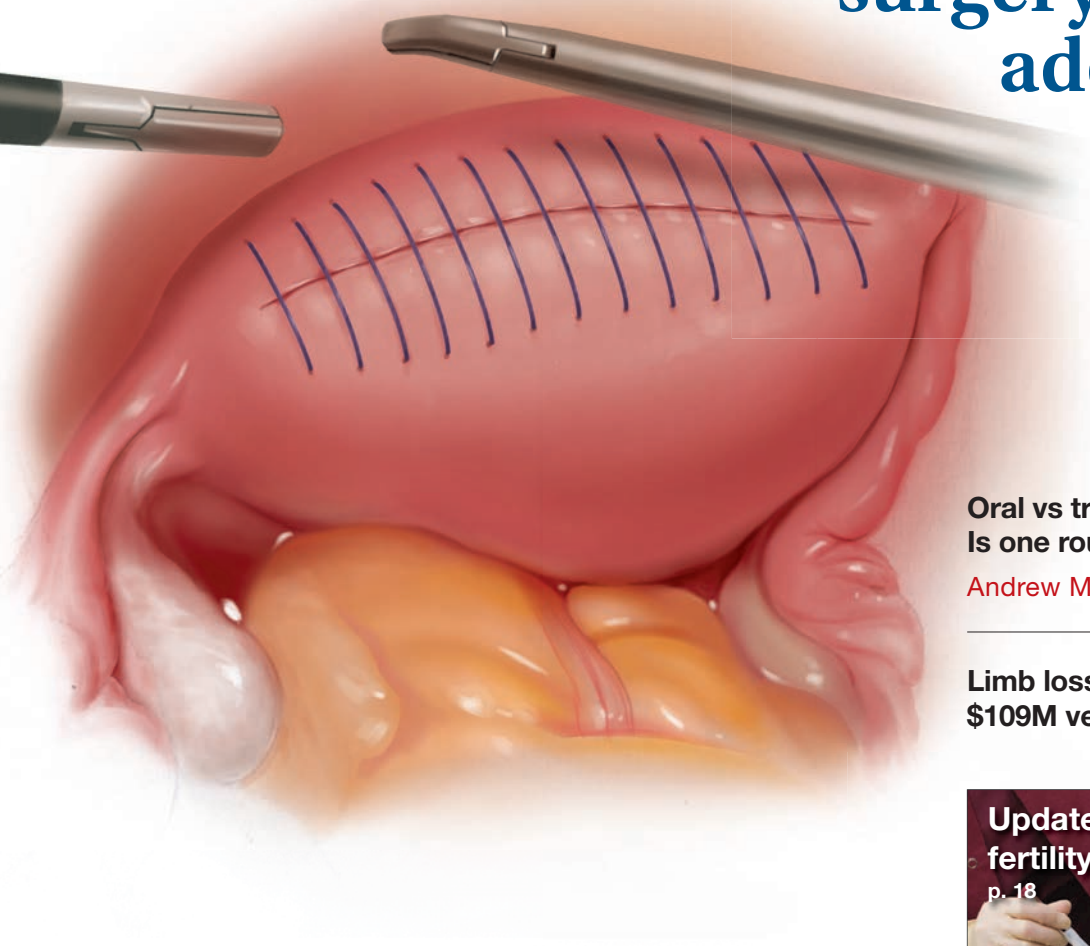
Offer most women labor induction by 41 weeks
Robert L. Barbieri, MD

Uterine aspiration: From OR to office

New data on vaginal estrogen and chronic disease
JoAnn V. Pinkerton, MD

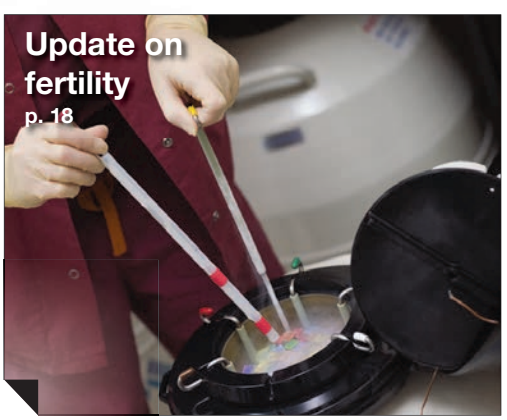
Uterine sparing surgery for severe adenomyosis

Camran Nezhat, MD, and colleagues



Oral vs transdermal estrogen: Is one route safer?
Andrew M. Kaunitz, MD

Limb loss postcystectomy: $109M verdict



For your patients with moderate to severe dyspareunia due to menopause,

IT'S WHAT'S INSIDE THAT COUNTS

Only INTRAROSA® converts to androgens and estrogens in a woman's body with no restrictions on duration of use[1]*

Help give women with moderate to severe dyspareunia due to menopause the chance to embrace the next third of their lives.

- First and only FDA-approved, vaginal non–estrogen-based therapy[1,2]
- Demonstrated efficacy[1-3]
- Once-daily treatment at bedtime[1]

*Prasterone is an inactive precursor that is converted into active androgens and estrogens. The mechanism of action is not fully established.

Order samples and learn more at IntrarosaHCP.com.

Intrarosa® Prasterone VAGINAL INSERTS 6.5 mg

INSPIRED BY HER BODY

Indication

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

Important Safety Information

INTRAROSA is contraindicated in women with undiagnosed abnormal genital bleeding.

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

In four 12-week randomized, placebo-controlled clinical trials, the most common adverse reaction with an incidence ≥2 percent was vaginal discharge. In one 52-week open-label clinical trial, the most common adverse reactions with an incidence ≥2 percent were vaginal discharge and abnormal Pap smear.

Please see the following page for a Brief Summary of full Prescribing Information.

References: 1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2018. **2.** Archer DF, Labrie F, Bouchard C, et al. *Menopause*. 2015;22(9):950-963. **3.** Labrie F, Archer DF, Koltun W, et al. *Menopause*. 2016;23(3):243-256.

amag PHARMACEUTICALS

Intrarosa®
Prasterone VAGINAL INSERTS 6.5 mg

INTRAROSA® (prasterone) vaginal inserts

Brief Summary: Consult full Prescribing Information for complete product information.

INDICATION

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

CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment with INTRAROSA.

WARNINGS AND PRECAUTIONS Current or Past History of Breast Cancer

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

ADVERSE REACTIONS Clinical Trials Experience

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

In four (4) placebo-controlled, 12-week clinical trials [91% - White Caucasian non-Hispanic women, 7% - Black or African American women, and 2% - "Other" women, average age 58.8 years of age (range 40 to 80 years of age)], vaginal discharge is the most frequently reported treatment-emergent adverse reaction in the INTRAROSA treatment group with an incidence of ≥ 2 percent and greater than reported in the placebo treatment group. There were 38 cases in 665 participating postmenopausal women (5.71 percent) in the INTRAROSA treatment group compared to 17 cases in 464 participating postmenopausal women (3.66 percent) in the placebo treatment group.

In a 52-week non-comparative clinical trial [92% - White Caucasian non-Hispanic women, 6% - Black or African American women, and 2% - "Other" women, average age 57.9 years of age (range 43 to 75 years of age)], vaginal discharge and abnormal Pap smear at 52 weeks were the most frequently reported treatment-emergent adverse reaction in women receiving INTRAROSA with an incidence of ≥ 2 percent. There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear (2.1 percent) in 521 participating postmenopausal women. The eleven (11) cases of abnormal Pap smear at 52 weeks include one (1) case of low-grade squamous intraepithelial lesion (LSIL), and ten (10) cases of atypical squamous cells of undetermined significance (ASCUS).

amag PHARMACEUTICALS

Manufactured for: Endoceutics, Inc., Quebec City, Canada, G1V 4M7.
Distributed by: AMAG Pharmaceuticals, Inc., Waltham, MA 02451
PP-INR-US-00250

#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 2018, Obstetrics/Gynecology Combined Office & Hospital Readers.

The trustworthy reputation of the UltraPulse® Encore is now available on UltraPulse DUO enhancing its performance with the addition of FiberLase™ CO_2 Fiber.

Not all DUOs are the same

- Lumenis UltraPulse DUO is the Gold standard technology when it comes to ultra-precise tissue-laser interaction – And we'll teach you how to use it!
- It combines the best of all worlds into one surgical platform – FiberLase and Free beam on one system
- It's a true innovation that will allow better patient care and recovery

Customize it for your Needs

- Seamlessly alternate between the CO_2 energy delivery methods to obtain both precision and access
- Address unexpected challenges: With the vital combination of the fiber and articulated arm and complete the procedure without the need for additional operations and hospitalization
- Optimize pulse parameters to maintain zero char free margins

"When it comes to fertility surgery, we have to work around very delicate tissue and spare as much healthy tissue as possible. Few tools offer precision of the CO_2 laser to help me excise only the tissue of interest and perform extremely meticulous dissections. It's a staple in my practice; I use it in every operative case that I perform."

Ken Sinervo, M.D.
Medical Director of the Center for Endometriosis Care
Atlanta, Georgia, USA.

Gynecology
(including laparoscopy and robotic assisted surgery)

Endometriosis, Excision/lysis of adhesions, Uterine myomas and fibroids, Ovarian fibromas and follicle cysts. Uterosacral ligament ablation, Hysterectomy, Conization of the cervix

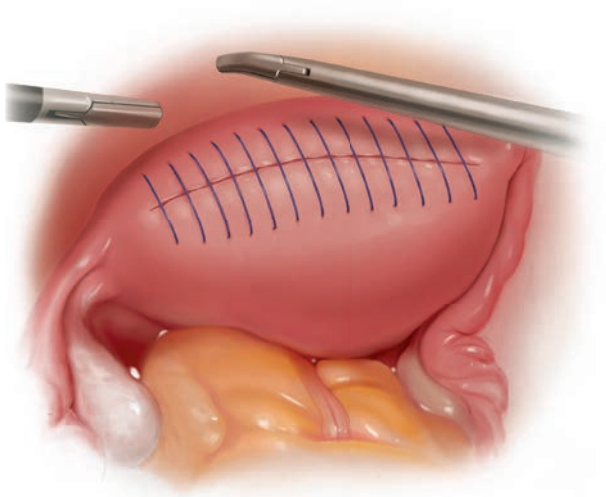
Flexibility & Simplicity
FiberLase™
CO_2 Fiber

BOOK A DEMO TODAY AND OFFER MORE TO YOUR PATIENTS:
877-LUMENIS | Surgical.USA@Lumenis.com | www.lumenis.com

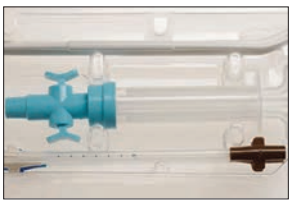
Lumenis®
Energy to Healthcare

FEBRUARY 2019 | VOL 31, NO 2

OBG MANAGEMENT



Avoiding late-term pregnancy **10**



Uterine aspiration **38**

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.

OBG MANAGEMENT (ISSN 1044-307x) is published monthly by Frontline Medical Communications Inc, 7 Century Drive, Suite 302, Parsippany, New Jersey 07054. The contents of this publication may not be reproduced in whole or part without the written consent of the owner. 2019 subscription rates (includes full-text access to mdedge.com/obgyn): United States: $162.00; elsewhere: $211.00. Single copy orders must be prepaid: United States: $27.00; Canada/Mexico: $33.00; other: $38.00. Periodicals postage paid at Parsippany, NJ, and additional mailing offices. Orders and Claims: OBG Management, Subscription Service, P.O. Box 3000, Denville, NJ 07834-3000, phone (833) 836-2705, or e-mail custsvc.obgm@fulcoinc.com. POSTMASTER: Please send address changes to OBG Management Subscription Service, 10255 W. Higgins Road, Suite 280, Rosemont, IL 60018-9914.

COVER IMAGE: KIMBERLY MARTENS

ON THE WEB
at mdedge.com/obgyn

WEB EXCLUSIVES

Epidural use in the United States—Statewide findings

Nationwide implementation of MIS reduced complications and increased survival in early-stage endometrial cancer

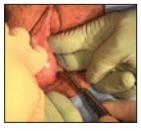
Visit us online for daily news

VIDEO LIBRARY

Instructional video for 4th-degree obstetric laceration repair using modified beef tongue model

JOSEPH MALEK, MD; JANA D. ILLSTON, MD; ALICIA C. BALLARD, MD; HOLLY E. RICHTER, PHD, MD

Brought to you by the Society of Gynecologic Surgeons



Excision of a Bartholin gland cyst

LISA R. GABOR, MD; PATRICIA J. MATTINGLY, MD; AND JIN HEE KIM, MD

Watch these, and more, expert surgical technique and commentary videos in the EXPLORE: Multimedia section online

MDedge | FRONTLINE MEDICAL COMMUNICATIONS
7 Century Drive, Suite 302
Parsippany, NJ 07054-4609
www.mdedge.com

BPA WORLDWIDE | AMM Association of Medical Media

Reader services. Address correspondence to OBG MANAGEMENT®, 7 Century Drive, Suite 302, Parsippany, NJ 07054.

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

LARC = long-acting reversible contraceptive

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

WOMN-1267530-0000 09/18

NEXPLANON is the only non-uterine LARC option

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

- Provides Up to **3 years** of pregnancy prevention*
- **>99%** effective†
- **Reversible** if her plans change

Placed subdermally in the inner upper arm just under the skin

(Actual implant shown; actual implant is 4 cm)

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

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

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

1. **Complications of Insertion and Removal**

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

   If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissues. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

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

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

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

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

2. **Changes in Menstrual Bleeding Patterns**

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

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

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

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

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

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

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

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

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

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

3. **Ectopic Pregnancies**

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

4. **Thrombotic and Other Vascular Events**

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

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

5. **Ovarian Cysts**

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

6. **Carcinoma of the Breast and Reproductive Organs**

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

7. **Liver Disease**

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

8. **Weight Gain**

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

9. **Elevated Blood Pressure**

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

10. **Gallbladder Disease**

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

11. **Carbohydrate and Lipid Metabolic Effects**

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

12. **Depressed Mood**

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

13. **Return to Ovulation**

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

14. **Fluid Retention**
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.
15. **Contact Lenses**
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.
16. ***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration].*
17. **Monitoring**
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.
18. **Drug-Laboratory Test Interactions**
Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives

Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or ncrease breakthrough bleeding.

Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

1. **Pregnancy**
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant *[see Contraindications].* Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.
2. **Nursing Mothers**
Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.
3. **Pediatric Use**
Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.
4. **Geriatric Use**
This product has not been studied in women over 65 years of age and is not indicated in this population.
5. **Hepatic Impairment**
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications].*
6. **Overweight Women**
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*

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

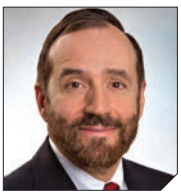
Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1705r019
Revised: 05/17

EDITORIAL

How do you feel about expectantly managing a well-dated pregnancy past 41 weeks' gestation?

Most women with a well-dated pregnancy should be offered the option of induction of labor before or at 41 weeks' gestation



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

Most people know that preterm birth is a major contributor to perinatal morbidity and mortality. Consequently, strict guidelines have been enforced to prevent non–medically indicated scheduled deliveries before 39 weeks' gestation. Fewer people recognize that late-term birth is also an important and avoidable contributor to perinatal morbidity. To improve pregnancy outcomes, we may need enhanced guidelines about minimizing expectant management of pregnancy beyond 41 weeks' gestation.

For the fetus, what is the optimal duration of a healthy pregnancy?

When pregnancy progresses past the date of the confinement, the risk of fetal or newborn injury or death increases, especially after 41 weeks' gestation. Analysis of this risk, day by day, suggests that after 40 weeks' and 3 days' gestation there is no medical benefit to the fetus to remain in utero because, compared with induced delivery, expectant management of the pregnancy is associated with a greater rate of fetal and newborn morbidity and mortality.[1]

The fetal and newborn benefits of delivery, rather than expectant management, at term include: a decrease in stillbirth and perinatal death rates, a decrease in admissions to the neonatal intensive care unit (NICU), a decrease in meconium-stained amniotic fluid and meconium aspiration syndrome, a decrease in low Apgar scores, and a decrease in problems related to uteroplacental insufficiency, including oligohydramnios.[2] In a comprehensive meta-analysis, induction of labor at or beyond term reduced the risk of perinatal death or stillbirth by 67%, the risk of a 5-minute Apgar score below 7 by 30%, and the risk of NICU admission by 12%.[2] The number of women that would need to be induced to prevent 1 perinatal death was estimated to be 426.[2]

Maternal benefits of avoiding late-term pregnancy

The maternal benefits of avoiding continuing a pregnancy past 41 weeks' gestation include a reduction in labor dystocia and the risk of cesarean delivery (CD).[2,3] In one clinical trial, 3,407 women with low-risk pregnancy were randomly assigned to induction of labor at 41 weeks' gestation or expectant management, awaiting the onset of labor with serial antenatal monitoring (nonstress tests and assessment of amniotic fluid volume).[4] The CD rate was lower among the women randomized to induction of labor at 41 weeks' (21.2% vs 24.5% in the expectant management group, P = .03). The rate of meconium-stained fluid was lower in the induction of labor group (25.0% vs 28.7%, P = .009). The rate of CD due to fetal distress also was lower in the induction of labor group (5.7% vs 8.3%, P = .003). The risks of maternal postpartum hemorrhage, sepsis, and endometritis did not differ between the groups. There were 2 stillbirths in the expectant management group (2/1,706) and none in the induction of labor group (0/1,701). There were no neonatal deaths in this study.[4]

Obstetric management, including accurate dating of pregnancy and membrane sweeping at term, can help to reduce the risk that a pregnancy will progress beyond 41 weeks' gestation.[5]

CONTINUED ON PAGE 12

Enhancing patient outcomes, managing costs, and optimizing delivery of care.

The value of care:
VAGINITIS TESTING

LabCorp's NuSwab® portfolio combines cost-effective, clinically relevant, research-driven testing with the convenience of a single-swab collection and is a targeted approach to testing for bacterial vaginosis, yeast (*Candida*), and four common STDs.

Amplified molecular target testing (NuSwab) has been shown to exceed non-amplified testing by:[1]

- Identifying an additional 20-25% of symptomatic patients with suspected vulvovaginitis (VV). Which in turn helps:
  - Lower odds of preterm labor or delivery for symptomatic pregnant patients by 15%
  - Lower per patient expenditure of $268 during follow up period
  - Lower odds of all-cause hospitalization by 22%

Value beyond testing.

For more information, please visit
*www.labcorp.com/**value-care-vaginitis***

LabCorp

1. Ackerman SJ, Wahl PM, Knight T, Cartwright, CP. Healthcare Resource Utilization and Costs of Amplified Versus Non-amplified Molecular Probe Testing for Vaginitis/Vaginosis: A U. S. Commercial Payer Perspective. LabCorp.

CONTINUED FROM PAGE 10

Routinely use ultrasound to accurately establish gestational age

First trimester ultrasound should be offered to all pregnant women because it is a more accurate assessment of gestational age and will result in fewer pregnancies that are thought to be at or beyond 41 weeks' gestation.[5] In a meta-analysis of 8 studies, including 25,516 women, early ultrasonography reduced the rate of intervention for postterm pregnancy by 42% (31/1,000 to 18/1,000 pregnant women).[6]

Membrane sweeping (or stripping)

Membrane sweeping, which causes the release of prostaglandins, has been reported to reduce the risk of late-term and postterm induction of labor.[7,8] In the most recent Cochrane review on the topic, sweeping membranes reduced the rate of induction of labor at 41 weeks by 41% and at 42 weeks by 72%.[7] To avoid one induction of labor for late-term or postterm pregnancy, sweeping of membranes would need to be performed on 8 women. In a recent meta-analysis, membrane sweeping reduced the rate of induction of labor for postmaturity by 48%.[9]

Membrane sweeping is associated with pain and an increased rate of vaginal bleeding.[10] It does not increase the rate of maternal or neonatal infection, however. It also does not reduce the CD rate. In the United Kingdom, the National Institute for Health and Clinical Excellence recommends that all clinicians have a discussion of membrane sweeping with their patients at 38 weeks' gestation and offer membrane stripping at 40 weeks to increase the rate of timely spontaneous labor and to avoid the risks of prolonged pregnancy.[11] Of note, in one randomized study of women planning a trial of labor after CD, membrane sweeping did not impact the duration of pregnancy, onset of spontaneous labor, or the CD rate.[12]

Steps from an expert. A skillfull midwife practicing in the United Kingdom provides the following guidance on how to perform membrane sweeping.[13]

1. Prepare the patient. Explain the procedure, have the patient empty her bladder, and encourage relaxed breathing if the vaginal examination causes pain.
2. Abdominal exam. Assess uterine size, fetal lie and presentation, and fetal heart tones.
3. Vaginal exam. Ascertain cervical dilation, effacement, and position. If the cervix is closed a sweep may not be possible. In this case, massaging the vaginal fornices may help to release prostaglandins and stimulate uterine contractions. If the cervix is closed but soft, massage of the cervix may permit the insertion of a finger. If the cervix is favorable for sweeping, insert one finger in the cervix and rotate the finger in a circle to separate the amnion from the cervix.
4. After the procedure. Provide the woman with a sanitary pad and recommend acetaminophen and a warm bath if she has discomfort or painful contractions. Advise her to come to the maternity unit in the following situations: severe pain, significant bleeding, or spontaneous rupture of the membranes.

Membrane sweeping can be performed as frequently as every 3 days. Formal cervical ripening and induction of labor may need to be planned if membrane sweeping does not result in the initiation of regular contractions.

Collaborative decision making

All clinicians recognize the primacy of patient autonomy.[14] Competent patients have the right to select the course of care that they believe is optimal. When a patient decides to continue her pregnancy past 41 weeks, it is helpful to endorse respect for the decision and inquire

about the patient's reasons for continuing the pregnancy. Understanding the patient's concerns may begin a conversation that will result in the patient accepting a plan for induction near 41 weeks' gestation. If the patient insists on expectant management well beyond 41 weeks, the medical record should contain a summary of the clinician recommendation to induce labor at or before 41 weeks' gestation and the patient's preference for expectant management and her understanding of the decision's risks.

Obstetricians and midwives constantly face the challenge of balancing the desire to avoid meddlesome interference in a pregnancy with the need to act to prevent adverse pregnancy outcomes. The challenge is daunting. A comprehensive meta-analysis of the benefit of induction of labor at or beyond term, estimated that 426 inductions would need to be initiated to prevent one perinatal death.[2] From one perspective it is meddlesome to intervene on more than 400 women to prevent one perinatal death. However, substantial data indicate that expectant management of a well-dated pregnancy at 41 weeks' gestation will result in adverse outcomes that likely could be prevented by induction of labor. If you ran an airline and could take an action to prevent one airplane crash for every 400 flights, you would likely move heaven and earth to try to prevent that disaster. Unless the patient strongly prefers expectant management, well-managed induction of labor at or before 41 weeks' gestation is likely to reduce the rate of adverse pregnancy events and, hence, is warranted. ●

RBARBIERI@MDEDGE.COM

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

References

1. Divon MY, Ferber A, Sanderson M, et al. A functional definition of prolonged pregnancy based on daily fetal and neonatal mortality rates. *Ultrasound Obstet Gynecol*. 2004;23:423-426.
2. Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev*. 2018;5:CD004945.
3. Caughey AB, Sundaram V, Kaimal AJ, et al. Systematic review: elective induction of labor versus expectant management of pregnancy. *Ann Intern Med*. 2009;151:252-263.
4. Hannah ME, Hannah WJ, Hellmann J, et al; Canadian Multicenter Post-term Pregnancy Trial Group. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. *N Engl J Med*. 1992;326:1587-1592.
5. Delaney M, Roggensack A. No. 214-Guidelines for the management of pregnancy at 41+0 to 42+0 weeks. *J Obstet Gynaecol Can*. 2017;39:e164-e174.
6. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev*. 2015;7:CD007058.
7. Boulvain M, Stan C, Irion O. Membrane sweeping for induction of labour. *Cochrane Database Syst Rev*. 2005;1:CD000451.
8. Berghella V, Rogers RA, Lescale K. Stripping of membranes as a safe method to reduce prolonged pregnancies. *Obstet Gynecol*. 1996;87:927-931.
9. Avdiyovski H, Haith-Cooper M, Scally A. Membrane sweeping at term to promote spontaneous labour and reduce the likelihood of a formal induction of labour for postmaturity: a systematic review and meta-analysis. *J Obstet Gynaecol*. 2018:1-9.
10. de Miranda E, van der Bom JG, Bonsel G, et al. Membrane sweeping and prevention of post-term pregnancy in low-risk pregnancies: a randomised controlled trial. *BJOG*. 2006;113:402-408.
11. National Collaborating Centre for Women's and Children's Health. NICE Guideline 70. Induction of labour; July 2008. https://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-full-guideline2. Accessed January 23, 2019.
12. Hamdan M, Sidhu K, Sabir N, et al. Serial membrane sweeping at term in planned vaginal birth after cesarean: a randomized controlled trial. *Obstet Gynecol*. 2009;114:745-751.
13. Gibbon K. How to perform a stretch and sweep. *Midwives Magazine*. 2012. https://www.rcm.org.uk/news-views-and-analysis/analysis/how-to%E2%80%A6-perform-a-stretch-and-sweep. Accessed January 23, 2019.
14. Ryan KJ. Erosion of the rights of pregnant women: in the interest of fetal well-being. *Womens Health Issues*. 1990;1:21-24.

Does the type of menopausal HT used increase the risk of venous thromboembolism?

Yes, according to a case-control study that analyzed data from 2 large UK databases in which 80,396 women aged 40 to 79 with a primary diagnosis of venous thromboembolism (VTE) between 1998 and 2017 were matched to 391,494 controls. Use of **oral conjugated equine estrogen (CEE) or estradiol was associated with an elevated risk of VTE** (odds ratio [OR], 1.49 and 1.27, respectively), while **transdermal preparations were safest (OR, 0.96) when risk of VTE was assessed**.

FAST TRACK

UK researchers identified 80,396 women with VTE matched to 391,494 controls to assess the association between VTE and different types of HT

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

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.

The Women's Health Initiative trials, in which menopausal women were randomly assigned to treatment with oral CEE or placebo, found that statistically the largest risk associated with menopausal hormone therapy (HT) was increased VTE.[1] Recently, investigators in the United Kingdom (UK) published results of their research aimed at determining the association between the risk of VTE and the use of different types of HT.[2]

The author reports receiving grant or research support from Allergan, Bayer, and Mithra and that he is a consultant to AMAG, Merck, and Pfizer.

Details of the study

Vinogradova and colleagues used 2 UK primary care research databases, QResearch and Clinical Practice Research Datalink, to identify cases of incident VTE in general practice records, hospital admissions, and mortality records. They identified 80,396 women (aged 40 to 79 years) diagnosed with VTE between 1998 and 2017 and 391,494 control women matched by age and general practice. The mean age of the case and control women was approximately 64 years; the great majority of women were white. Analyses were adjusted for smoking, body mass index (BMI), family history of VTE, and comorbidities associated with VTE.

Types of HT used. The investigators found that 5,795 (7.2%) women with VTE and 21,670 (5.5%) controls were exposed to HT in the 90 days before the index date (the first date of VTE diagnosis for cases became the

CONTINUED ON PAGE 16

femVue®

In-office **tubal patency** diagnostic test

Sono HSG with FemVue allows you to provide your patients with a

convenient, ultrasound-based tubal patency evaluation.

Expand your practice services while saving your patients **time** and **expense**.

Clinical studies have shown the diagnostic accuracy of Sono HSG to be concordant with fluoroscopic HSG.*

Become a FemVue provider by calling Femasys at

877.336.2562

or visit **www.femvue.com** to learn more.

00195:02 13.Sept.2018

*S. Maheux-Lacroix et al. Hum Reprod 2014;29(5):953-63.

CONTINUED FROM PAGE 14

index date for matched controls). In those exposed to HT:

- 4,915 (85%) cases and 16,938 (78%) controls used oral preparations (including 102 [1.8%] cases and 312 [1.4%] controls who also had transdermal preparations)
- 880 (14%) cases and 4,731 (19%) controls used transdermal HT only.

Association of VTE with HT. Risk of VTE was increased with all oral HT formulations, including combined (estrogen plus progestogen) and estrogen-only preparations. Use of oral CEE (odds ratio [OR], 1.49) and estradiol (OR, 1.27) were both associated with an elevated risk of VTE ($P<.05$ for both comparisons). In contrast, use of transdermal estradiol (the great majority of which was administered by patch) was not associated with an elevated risk of VTE (OR, 0.96).

Direct comparison of oral estradiol and CEE found that the lower VTE risk with oral estradiol achieved statistical significance ($P = .005$). Direct comparison of oral and transdermal estrogen revealed an OR of 1.7 for the oral route of administration ($P<.001$)

FAST TRACK

Elevated risk of VTE was associated with use of oral CEE (OR, 1.49) and oral estradiol (OR, 1.27) but not with transdermal estradiol (OR, 0.96)

Study strengths and weaknesses

This study used data from the 2 largest primary care databases in the United Kingdom. Analyses were adjusted for numerous confounding factors, including acute and chronic conditions, lifestyle factors, and social deprivation. Additional sensitivity analyses were conducted and yielded results similar to those of the main analysis.

Several limitations could have resulted in some residual confounding bias. For example, drug exposure information was based on HT prescriptions and not actual use; data on some factors were not available, such as indications for HT, age at menopause, and education level; and for a small proportion of women, some data (smoking status, alcohol consumption, BMI) were missing and had to be imputed for analysis. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although randomized trials have not compared VTE risk with oral versus transdermal estrogen, prior observational studies have consistently suggested that transdermal estrogen does not elevate VTE risk; this is consistent with the results from this large UK study. In my practice, congruent with the authors' suggestions, I recommend transdermal rather than oral estrogen for patients (notably, those who are obese) who at baseline have risk factors for VTE. For menopausal women for whom use of oral estrogen is indicated, I recommend estradiol rather than CEE, since estradiol is less expensive and, based on this study's results, may be safer than CEE.

ANDREW M. KAUNITZ, MD

References

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353-1368.
2. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2019;364:k4810.

DON'T MISS...

Dr. JoAnn V. Pinkerton's Examining the Evidence:

›› **Is vaginal estrogen used for GSM associated with a higher risk of CVD or cancer?** page 52

iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Cohort 1		Cohort 2	
	Injectafer (N=244)	Oral Iron (N=251)	Injectafer (N=245)	IV SC[a] (N=237)
Baseline	10.6 (1.0)	10.6 (1.0)	9.1 (1.6)	9.0 (1.5)
Highest Value	12.2 (1.1)	11.4 (1.2)	12.0 (1.2)	11.2 (1.3)
Change (from baseline to highest value)	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
p-value	0.001		0.001	

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2 ± 224.2 ng/mL in Cohort 1 and 218.2 ± 211.4 ng/mL in Cohort 2), and transferrin saturation (13 ± 16% in Cohort 1 and 20 ± 15% in Cohort 2) were observed at Day 35 in Injectafer-treated patients.

14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease

Trial 2: REPAIR-IDA, Randomized Evaluation of efficacy and safety of Ferric carboxymaltose in Patients with iron deficiency Anemia and Impaired Renal function, (NCT00981045) was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) $\leq$ 11.5 g/dL, ferritin $\leq$ 100 ng/mL or ferritin $\leq$ 300 ng/mL when transferrin saturation (TSAT) $\leq$ 30%. Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 101); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Injectafer (N=1249)	Venofer (N=1244)
Baseline	10.3 (0.8)	10.3 (0.8)
Highest Value	11.4 (1.2)	11.3 (1.1)
Change (from baseline to highest value)	1.1 (1.0)	0.9 (0.92)
Treatment Difference (95% CI)	0.21 (0.13, 0.28)	

Increases from baseline in mean ferritin (734.7 ± 337.8 ng/mL), and transferrin saturation (30 ± 17%) were observed prior to Day 56 in Injectafer-treated patients.

17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*].

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

IN0650
RQ1052-B Revised: 04/2018

LAST CHANCE!

13.25 *AMA PRA Category 1 Credits*™ | 13.25 Pharmacy Contact Hours
13.25 Nursing Contact Hours | 13.25 AAFP Prescribed Credits

ABIM CME MOC ACCREDITED

6TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

A CONTINUING MEDICAL EDUCATION CONFERENCE

March 15-16, 2019

The Westin Philadelphia | Philadelphia, Pennsylvania

PROGRAM CHAIR
Nikolaos T. Pyrsopoulos, MD, PhD, MBA, FACP, AGAF, FAASLD, FRCP (Edin)
Professor of Medicine and Chief, Division of Gastroenterology and Hepatology
Professor of Physiology, Pharmacology and Neuroscience
Rutgers New Jersey Medical School
Medical Director Liver Transplantation
University Hospital
Newark NJ

TOPICS

- Hepatitis B & C
- Liver Cancer
- Irritable Bowel Syndrome
- Gastroesophageal Reflux Disorder
- Inflammatory Bowel Disease
- NASH
- Colorectal Cancer Screening
- Primary Biliary Cholangitis
- Gut Microbiota and Liver Disease
- Liver Transplant

and more!

Jointly provided by RUTGERS New Jersey Medical School and Global Academy for Medical Education

Publication partners: Family Practice News. Internal Medicine News.

TO REGISTER AND LEARN MORE GO TO:
GlobalAcademyCME.com/DDNA

UPDATE Fertility

G. David Adamson, MD
Dr. Adamson is Founder and CEO of Advanced Reproductive Care, Inc (ARC Fertility); Clinical Professor, ACF, at Stanford University School of Medicine; and Associate Clinical Professor at the University of California, San Francisco. He is also Director of Equal3 Fertility, APC in Cupertino, California.

Max Ezzati, MD
Dr. Ezzati is a Board-certified reproductive endocrinology and infertility (REI) specialist and the Medical Director of Department of Reproductive Endocrinology and Infertility at Palo Alto Medical Foundation Fertility Physicians of Northern California.

Dr. Adamson reports being a consultant to Abbott, AbbVie, Ferring, Guerbet, Hernest, and Merck, and that he has equity in ARC Fertility. Dr. Ezzati reports no financial relationships relevant to this article.

Progress is being made in recognizing infertility as a disease (thus meriting insurance coverage) and in improving embryo selection techniques for IVF treatment, but more work is needed. Plus, the SART's redesigned report includes a new feature for calculating a personalized prognosis that can aid in treatment decision making. Two fertility experts boil down these complex issues.

IN THIS ARTICLE

Professional societies, global organizations, and advocacy groups are continually working toward the goal of having the costs of infertility care covered by insurance carriers. Paramount to that effort is obtaining recognition of infertility as a burdensome disease. In this Update, we summarize national and international initiatives and societal trends that are helping to move us closer to that goal, and we encourage ObGyns to lead advocacy efforts.

Next, we detail several notable new features available in the annual report of the Society for Assisted Reproductive Technology (SART), an online interactive document that can be used to assist clinicians and patients in treatment decisions.

We also tackle the complexities of embryo selection for in vitro fertilization (IVF) and describe a potentially promising aneuploidy screening test, and explore its limitations.

PHOTO: SHUTTERSTOCK

Advances in recognizing infertility as a disease that merits insurance coverage

Article 16 of the United Nations Declaration of Human Rights states that "Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and to found a family. They are entitled to equal rights as

TABLE 1 How infertility is defined by the international glossary on infertility and fertility care[2]

Definition
Infertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner. Fertility interventions may be initiated in less than 1 year based on medical, sexual and reproductive history, age, physical findings, and diagnostic testing. Infertility is a disease, which generates disability as an impairment of function.

Supporters of infertility as a disease

- American Medical Association
- American Society for Reproductive Medicine
- European Society of Human Reproduction and Embryology
- International Federation of Fertility Societies
- International Federation of Gynecology and Obstetrics
- March of Dimes
- World Health Organization
- Multiple other global and regional professional societies

to marriage, during marriage and at its dissolution."[1] While few people value anything more than their family, the inability to have one because of infertility has long been in the shadows. Infertility is surrounded by myth, poorly understood by the public, rarely discussed in polite company, badly managed by physicians, and rarely covered by insurance. The current inadequacy of infertility insurance coverage denies the basic human right to found a family and perpetuates gender inequalities.

Major reproductive medicine organizations globally have endorsed the definition of infertility as a disease that "generates disability as an impairment of function" (**TABLE 1**).[2] Fortunately, medical, societal, and judicial changes have resulted in progress for the 6.1 million women (and equivalent number of men) affected by infertility in the United States.[3]

Professional group advocacy efforts, and judicial rulings

The World Health Organization (WHO) has addressed infertility over the past several decades, with the organization's standards on semen analysis being the most recognized outcome. Progress has been limited, however, regarding global or national policy that recognizes the importance of infertility as a medical and public health problem.

In 2009, the glossary published by the WHO with the International Committee for Monitoring Assisted Reproductive Technology (ICMART) defined infertility as a disease.[4] This recognition is important because it aids policy making, insurance coverage, and/or other payments for services.

The WHO also has begun the process of developing new infertility guidelines. Recently, the WHO held a summit on safety and access to fertility care, which was attended by many representatives of nation-state governments and international experts. It is hoped that a document from those proceedings will reinforce the public health importance of infertility and support the need to promote equality in access to safe fertility care. WHO initiatives matter because they apply to nation-states.

In the United States, the American Society for Reproductive Medicine (ASRM) for many years has recognized infertility as a disease. Only in 2017, however, did delegates at the American Medical Association's annual meeting vote to support the WHO's designation of infertility as a disease.

FAST TRACK

The ASRM for many years has recognized infertility as a disease, but only in 2017 did AMA delegates support the WHO's designation of infertility as a disease

CONTINUED ON PAGE 20

CONTINUED FROM PAGE 19

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The time is now for ObGyns and other women's health care providers to advocate for insurance coverage of infertility care. When our patients have inadequate coverage, we should encourage them to take action by contacting their insurance company and their employers to explain the reasons and argue for better coverage. Also, contact RESOLVE for additional information.

Judicial views. In 1998, the US Supreme Court held that infertility is a disability under the Americans with Disabilities Act (ADA). The Court subsequently held, however, that a person is not considered disabled under the act if the disability can be overcome by mitigating or corrective measures. In 2000, a lower court held that, while infertility is a disability, an employer's health plan that excludes treatment for it is not discriminatory under the ADA if it applies to all employees.

Societal recognition. Interestingly, improved technology for oocyte cryopreservation has resulted in greater recognition of reproductive issues and the disparity in reproductive health societal norms and rights between men and women.

Media stories and gender issues in employment, especially in such high-profile industries as technology and finance, have highlighted long-standing inequities, many of which concern reproductive issues. These issues have been further disseminated by the #metoo movement. Some employers are beginning to respond by recognizing their employees' reproductive needs and providing improved benefits for reproductive care.

FAST TRACK

ObGyns and other women's health care providers can help continue the progress toward equality in reproductive rights, including access to infertility care

ObGyns must continue to lead advocacy

Not all has been progress. Personhood bills in several states threaten basic reproductive rights of women and men. The ASRM and RESOLVE (the National Infertility Association) have taken leading roles in opposing these legislative initiatives and supporting reproductive rights.[5]

Advocacy efforts through events and trends have resulted in gradually improving the recognition of the burden of infertility, inadequate insurance coverage, and continuing gender inequalities in reproduction. Today, patients, professionals, and national and international organizations are coalescing around demands for recognition, access to care, and gender and diversity equality. While much remains to be done, progress is being made in society, government, the workplace, and the health care system.

ObGyns and other women's health care providers can help continue the progress toward equality in reproductive rights, including access to infertility care, by discussing insurance inequities with patients, informing insurance companies that infertility is a disease, and encouraging patients to challenge inadequate and unequal insurance coverage of needed reproductive health care.

Latest SART report offers new features to aid in treatment decision making

Knowledge of the prognosis and its various treatment options is an important aspect of infertility treatment. The SART recently updated its annual Clinic Summary Report (CSR), which includes valuable new features for patients and physicians considering assisted reproductive technology (ART) treatment.[6]

SART compiles complex data and reports outcomes

The SART has been reporting IVF outcomes and other ART outcomes since 1988. The society's annual report is widely read by consumers, patients, physicians, and policy makers, and it has many important uses. However, the report is complicated and difficult to interpret for many reasons. For example, treatments are complex and varied (especially with application of new cryopreservation technology), and there are variations among clinics with respect to patient selection, protocols used, philosophy of practice, and numerous other variables.

Because of this, the SART states, "The SART Clinic Summary Report (CSR) allows patients to view national and individual clinic IVF success rates. The data presented in this report should not be used for comparing clinics. Clinics may have differences in patient selection and treatment approaches which may artificially inflate or lower pregnancy rates relative to another clinic. Please discuss this with your doctor."[6]

Nevertheless, the CSR is extremely useful because it reports outcomes, which can lead to more informed patients and physicians and thus better access to safe and effective use of ART. The SART has redesigned the CSR to make it more useful.

Redesigned CSR focuses on outcomes important to patients

In recent years, new technologies have increased dramatically the use of embryo cryopreservation, genetic testing, and single embryo transfer (SET). The new CSR format is more patient focused and identifies more directly the treatment burden: ovarian stimulation, egg retrieval, intracytoplasmic sperm injection, preimplantation genetic testing (PGT), cryopreservation, frozen embryo transfer, and multiple cycles. It also focuses on the important patient outcomes, including live birth of a healthy child, multiple pregnancy, number of cycles, and chances of success per patient over time (including both fresh and frozen embryo transfers).

Notable changes

A major change in the CSR is that there is a preliminary report for a given year and then a final report the following year. This helps to more accurately report cycles that have been "delayed" because of egg retrieval and embryo freezing performed in the reported year but then transferred in the following reporting year.

Cycle counting. A cycle is counted when a woman has started medications for an ART procedure or, in a "natural" cycle when no medications are used, the first day of menses of the ART cycle. If several cycles are performed to bank eggs or embryos, each will be counted in the denominator when calculating the pregnancy rate. This more accurately reflects the patient treatment burden and costs. A cycle cancelled before egg retrieval is still counted as a cycle.

Defining success. Success is characterized as delivery of a child, since this is the outcome patients desire. Singleton deliveries are emphasized, since twin and higher-order multiple pregnancies have a higher risk of prematurity, morbidity, mortality, and cost. The percentages of triplet, twin, and singleton births contributing to the live birth rate are provided for each cycle group, as is prematurity (**TABLE 2,** page 22).[6]

The end point of a treatment cycle can vary. The new CSR captures the success rate following one or more egg retrievals and the first embryo transfer (primary outcome), the success of subsequent cycles using frozen eggs or embryos not transferred in the first embryo transfer, and the combined contribution of the primary and subsequent cycles to the cumulative live birth rate for a patient both in the preliminary report and the final report for any given year. The live birth rate per patient also is reported and includes the outcomes for patients who are new to an infertility center and starting their first cycle for retrieval of their own eggs during the reporting year.

Outcomes and prognostic factors. Outcomes are reported by multiple factors, including patient age and source of the eggs. These are important prognostic factors; separating the data allows you to obtain a better

FAST TRACK

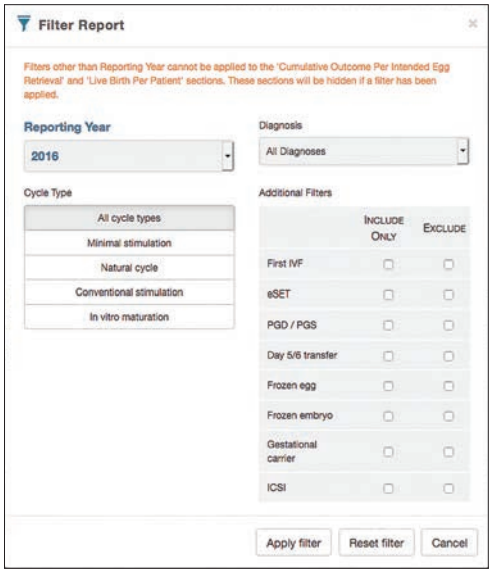
Success is characterized as delivery of a child, since this is the outcome patients desire

TABLE 2 SART 2016 preliminary assisted reproductive technology outcomes[6]

Preliminary cumulative outcome per egg retrieval cycle, using patient's own eggs					
	Age of woman				
	<35	35–37	38–40	41–42	>42
Number of cycle starts	44,899	24,645	23,842	12,427	9,797
Singletons	**39.4%**	**28.9%**	**18.8%**	**10.1%**	**3.1%**
Twins	8.1%	5.7%	3.0%	1.1%	0.2%
Triplets or more	0.2%	0.2%	0.1%	0.0%	0%
Live births (confidence range)	47.6% (47.2–48.1)	34.8% (34.2–35.4)	21.8% (21.3–22.4)	11.2% (10.6–11.7)	3.3% (3.0–3.7)

Abbreviation: SART, Society for Assisted Reproductive Technology.

FIGURE Filter report included in the SART National Summary Report[6]



The filter report, available from the "Filter" tab on the SART National Summary Report website menu bar, contains various factors that can be included or excluded for calculating outcomes.

idea of both national and individual clinic experience by these factors.

The CSR also contains filters for infertility diagnosis, stimulation type, and other treatment details (**FIGURE**).[6] The filter is a useful feature because multiple types of treatment can be included or excluded. The outcome of different treatment interventions can then be estimated based on outcomes from the entire sample of US patients with similar characteristics and interventions. This powerful tool can help patients and physicians choose the best treatment based on prognosis.

Personalized prognosis. An important new feature is the SART Patient Predictor (https://www.sartcorsonline.com/predictor/patient), a model that permits an individual patient to obtain a more personalized prognosis. While the SART predictor uses only basic patient information, such as age, body mass index, and diagnosis, its estimate is based on the entire US sample of reported ART experience and therefore can help patients in decision making. Furthermore, the predictor calculates percentages for the outcome of one transfer of 2 embryos, and 2 transfers of a single embryo, to demonstrate the advantages of SET that result in a higher live birth rate but a significantly lower multiple pregnancy rate.

Summing up

The SART's new CSR is extremely useful to patients and to any physician who cares for infertility patients. It can help users both understand the expected results from different ART treatments and enable better physician-patient communication and decision making.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The updated annual SART Clinic Summary Report is an exceptionally valuable and easy-to-use online tool for you and your infertility patients.

Embryo selection techniques refined with use of newer technologies

Since the introduction of IVF in 1978, the final cumulative live birth rates per cycle initiated for oocyte retrieval after all resulting embryos have been trasferred continue to rise, currently standing at 54% for women younger than age 35 in the United States.[7] A number of achievements have contributed to this remarkable success, namely, improvements in IVF laboratory and embryo culture systems, advances in cryopreservation technology, availability of highly effective gonadotropins and gonadotropin–releasing hormone analogues, improved ultrasound technology, and the introduction of soft catheters for atraumatic embryo transfers.

Treatment now focuses on improved embryo selection

Now that excellent success rates have been attained, the focus of optimizing efforts in fertility treatment has shifted to improving safety by reducing the rates of multiple pregnancy through elective single embryo transfer (eSET), reducing the rates of miscarriage, and shortening the time to live birth. Methods to improve embryo selection lie at the forefront of these initiatives. These vary and include extended culture to blastocyst stage, standard morphologic evaluation as well as morphokinetic assessment of embryonic development via time-lapse imaging, and more recently the reintroduction of preimplantation genetic testing for aneuploidy (PGT-A), formerly known as preimplantation genetic screening (PGS).

Chromosomal abnormalities of the embryo, or embryo aneuploidies, are the most common cause of treatment failure following embryo transfer in IVF. The proportion of embryos affected with aneuploidies significantly increases with advancing maternal age: 40% to 50% of blastocysts in women younger than age 35 and about 90% of blastocysts in women older than age 42.[8] The premise with PGT-A is to identify these aneuploid embryos and increase the chances of success per embryo transfer by transferring euploid embryos.

That concept was initially applied to cleavage-stage embryos through the use of fluorescence in situ hybridization (FISH) technology to interrogate a maximum of 5 to 9 chromosomes in a single cell (single blastomere); however, although initial results from observational studies were encouraging, subsequent randomized controlled studies unexpectedly showed a reduction in pregnancy rates.[9] This was attributed to several factors, including biopsy-related damage to the cleavage-stage embryo, inability of FISH technology to assess aneuploidies of more than 5 to 9 chromosomes, mosaicism, and technical limitations associated with single-cell analysis.

Second-generation PGT-A testing has promise, and limitations

The newer PGT-A tests the embryos at the blastocyst stage by using biopsy samples from the trophectoderm (which will form the future placenta); this is expected to spare the inner cell mass ([ICM] which will give rise to the embryo proper) from biopsy-related injury.

On the genetics side, newer technologies, such as array comparative genomic hybridization, single nucleotide polymorphism arrays, quantitative polymerase chain reaction, and next-generation sequencing, offer the opportunity to assess all 24 chromosomes in a single biopsy specimen. Although a detailed discussion of these testing platforms is beyond the scope of this Update, certain points are worth mentioning.

FAST TRACK

Chromosomal abnormalities of the embryo (aneuploidies) are the most common cause of treatment failure following embryo transfer in IVF

CONTINUED ON PAGE 24

PHOTO: SHUTTERSTOCK

CONTINUED FROM PAGE 23

All these technologies require some form of genetic material amplification (most commonly whole genome amplification or multiplex polymerase chain reaction) to increase the relatively scant amount of DNA obtained from a sample of 4 to 6 cells. These amplification techniques have limitations that can subsequently impact the validity of the test results.

Furthermore, there is no consistency in depth of coverage for various parts of the genome, and subchromosomal (segmental) copy number variations below 3 to 5 Mb may not be detected. The threshold used in bioinformatics algorithms employed to interpret the raw data is subject to several biases and is not consistent among laboratories. As a result, the same sample assessed in different laboratories can potentially yield different results.

In addition to these technical limitations, mosaicism can pose another biologic limitation, as the biopsied trophectoderm cells may not accurately represent the chromosomal makeup of the ICM. Also, an embryo may be able to undergo self-correction during subsequent stages of development, and therefore even a documented trophectoderm abnormality at the blastocyst stage may not necessarily preclude that embryo from developing into a healthy baby.

Standardization is needed. Despite widespread promotion of PGT-A, well-designed randomized clinical trials (RCTs) have not yet consistently shown its benefits in improving pregnancy rates or reducing miscarriage rates. Although the initial small RCTs in a selected group of good prognosis patients suggested a beneficial effect in ongoing pregnancy rates per transfer, the largest multicenter RCT to date did not show any improvement in pregnancy rates or reduction in miscarriage rates.[10] In that study, a post hoc subgroup analysis suggested a possible beneficial effect in women aged 35 to 40. However, those results must be validated and reproduced with randomization at the start of stimulation, with the primary outcome being the live birth rate per initiated cycle, instead of per transfer, before PGT-A can be adopted universally in clinical practice.

With all the above considerations, the ASRM has appropriately concluded that "the value of preimplantation genetic testing for aneuploidy (PGT-A) as a screening test for IVF patients has yet to be determined."[11]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Standardization of clinical and laboratory protocols and additional studies to assess the effects of PGT-A on live birth rates per initiated cycles are recommended before this new technology is widely adopted in routine clinical practice. In our practice, we routinely offer and perform extended culture to blastocyst stage and standard morphologic assessment. After a thorough counseling on the current status of PGT-A, about 15% to 20% of our patients opt to undergo PGT-A.

References

1. United Nations website. General Assembly resolution 217A: Declaration of human rights. December 10, 1948. http://www.un.org/en/universal-declaration-human-rights/. Accessed January 11, 2019.
2. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Fertil Steril.* 2017;108:393-406.
3. US Department of Health and Human Services Office on Women's Health website. Infertility. https://www.womenshealth.gov/a-z-topics/infertility. Accessed January 24, 2019.
4. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al; International Committee for Monitoring Assisted Reproductive Technology, World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril.* 2009;92:1520-1524.
5. RESOLVE: The National Infertility Association website. Opposing personhood: RESOLVE fights to keep fertility medical treatments legal in the US. https://resolve.org/get-involved/advocate-for-access/our-issues/opposing-personhood/. Accessed January 11, 2019.
6. Society for Assisted Reproductive Technology website. National summary report. 2016 Preliminary national data. https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2016 . Accessed January 12, 2019.
7. Society for Assisted Reproductive Technology website. National summary report 2015. https://www.sartcorsonline,com/rptCSR_PublicMultYear.aspx?reportingYear=2015. Accessed January 12, 2019.
8. Harton GL, Munne S, Surrey M, et al; PGD Practitioners Group. Diminished effect of maternal age on implantation after preimplantation genetic diagnosis with array comparative genomic hybridization. *Fertil Steril.* 2013;100:1695-1703.
9. Mastenbroek S, Twisk M, van Echten-Arends, et al. In vitro fertilization with preimplantation genetic screening. *N Engl J Med.* 2007;357:9-17
10. Munne S, Kaplan B, Frattarelli JL, et al. Global multicenter randomized controlled trial comparing single embryo transfer with embryo selected by preimplantation genetic screening using next-generation sequencing versus morphologic assessment [abstract O-43]. *Fertil Steril.* 2017;108(suppl):e19.
11. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. *Fertil Steril.* 2018;109:429-436.

Intimate partner violence, guns, and the ObGyn

Gun violence affects us all, let's not "stay in our lane"

Katherine Koniares, MD
Resident, Department of Obstetrics and Gynecology, Tufts Medical Center, Boston, Massachusetts

Megan L. Evans, MD, MPH
Assistant Professor, Tufts University School of Medicine; Associate Program Director, Department of Obstetrics and Gynecology, Tufts Medical Center

On the afternoon of November 19, 2018, Dr. Tamara O'Neal was shot and killed by her ex-fiancé outside Mercy Hospital and Medical Center in Chicago, Illinois. After killing Dr. O'Neal, the gunman ran into the hospital where he exchanged gunfire with police, killing a pharmacy resident and a police officer, before he was killed by officers.[1]

This horrific encounter between a woman and her former partner begs for a conversation about intimate partner violence (IPV). A data brief of The National Intimate Partner and Sexual Violence Survey was published in November 2018. According to this report, 30.6% of women experienced physical violence by an intimate partner in 2015, with 21.4% of women experiencing severe physical violence. In addition, 31.0% of men experienced physical violence by an intimate partner in 2015; 14.9% of men experienced severe physical violence.[2]

The authors report no financial relationships relevant to this article.

Intimate partner violence is "our lane"

The shooting at Mercy Hospital occurred amongst a backdrop of controversy between the National Rifle Association (NRA) and the medical community. On November 7, 2018, the NRA tweeted that doctors should "stay in their lane" with regard to gun control after a position paper from the American College of Physicians on reducing firearm deaths and injuries was published in the *Annals of Internal Medicine*.[3] Doctors from every field and from all over the country responded through social media by stating that treating bullet wounds and caring for those affected by gun violence was "their lane."[4]

It is time for us as a community to recognize that gun violence affects us all. The majority of mass shooters have a history of IPV and often target their current or prior partner during the shooting.[5] At this intersection of IPV and gun control, the physician has a unique role. We not only treat those affected by gun violence and advocate for better gun control but we also have a duty to screen our patients for IPV. Part of the sacred patient–physician relationship is being present for our patients when they need us most. The American College of Obstetricians and Gynecologists (ACOG) recommends that ObGyns screen patients for IPV at regular intervals and recognizes that it may take several conversations before a patient discloses her history of IPV.[6] Additionally, given the increased risk of gun injuries and death, it behooves us to also screen for gun safety in the home.

Ask patients about IPV, and ask again

The shooting at Mercy Hospital was a stark reminder that IPV can affect any of us. With nearly one-third of women and more than one-quarter of men experiencing IPV in their lifetime, action must be taken. The first step is to routinely screen patients for IPV, offering support and community resources (see "Screening for intimate partner violence" on page 26). The second step is to work to decrease the access perpetrators of IPV have to weapons with which to

Screening for intimate partner violence

There are numerous verified screening tools available to assess for intimate partner violence (IPV) for both pregnant and nonpregnant patients. Many recommended tools are accessible on the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/violenceprevention/pdf/ipv/ipvandsvscreening.pdf.

In our office, the tool most commonly used is a 3-part question assessing domestic violence and IPV. It is important to recognize IPV can affect everyone—all races and religions regardless of socioeconomic background, sexual orientation, and pregnancy status. All patients deserve screening for IPV, and it should never be assumed a patient is not at risk. During an annual gynecology visit for return and new patients or a new obstetric intake visit, we use the following script obtained from ACOG's Committee Opinion 518 on IPV[1]:

Because violence is so common in many women's lives and because there is help available for women being abused, I now ask every patient about domestic violence:

1. *Within the past year (or since you have become pregnant) have you been hit, slapped, kicked, or otherwise physically hurt by someone?*
2. *Are you in a relationship with a person who threatens or physically hurts you?*
3. *Has anyone forced you to have sexual activities that made you feel uncomfortable?*

If a patient screens positive, we assess their immediate safety. If a social worker is readily available, we arrange an urgent meeting with the patient. If offices do not have immediate access to this service, online information can be provided to patients, including the National Resource Center on Domestic Violence (https://nnedv.org/) and a toll-free number to the National Domestic Violence Hotline: 1-800-799-7233.

Additionally, we ask patients about any history of verbal, physical, or sexual violence with prior partners, family members, acquaintances, coworkers, etc. Although the patient might not be at immediate risk, prior experiences with abuse can cause fear and anxiety around gynecologic and obstetric exams. Acknowledging this history can help the clinician adjust his or her physical exam and support the patient during, what may be, a triggering experience.

As an additional resource, Dr. Katherine Hicks-Courant, a resident at Tufts Medical Center, in Boston, Massachusetts, created a tool kit for providers working with pregnant patients with a history of sexual assault. It can be accessed without login online under the Junior Fellow Initiative Toolkit section at http://www.acog.org.

Reference

1. American College of Obstetricians and Gynecologists. Committee Opinion No. 518: intimate partner violence. *Obstet Gynecol.* 2012;119:412-417.

enact violence—through legislation, community engagement, and using our physician voices.

States that have passed legislation that prohibits persons with active restraining orders or a history of IPV or domestic violence from possessing firearms have seen a decrease in IPV firearm homicide rates.[7] These policies can make a profound impact on the safety of our patients. Women who are in violent relationships are 5 times more likely to die if their partner has access to a firearm.[5]

#BreakTheCycle

The 116th Congress convened in January. We have an opportunity to make real gun legislation reform and work to keep our communities and our patients at risk for IPV safer. Tweet your representatives with #BreakTheCycle, and be on the lookout for important legislation to enact real change.

To sign the open letter from American Healthcare Professionals to the NRA regarding their recent comments and our medical experiences with gun violence, visit https://affirmresearch.org/this-is-our-lane-petition. Currently, there are more than 41,000 signatures. ●

References

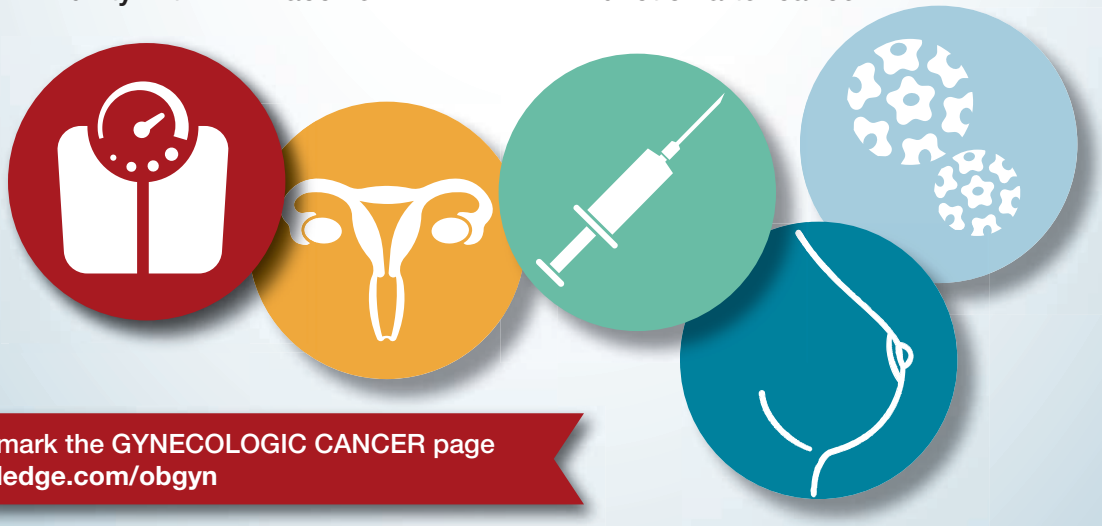
1. Buckley M, Gorner J, Greene M. Chicago hospital shooting: Young cop, doctor, pharmacy resident and gunman die in Mercy Hospital attack. *Chicago Tribune*. Nov. 20, 2018.
2. Smith SG, Zhang X, Basile KC, et al. The National Intimate Partner and Sexual Violence Survey (NISVS): 2015 data brief – updated release. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; November 2018.
3. Butkus R, Doherty R, Bornstein SS; for the Health and Public Policy Committee of the American College of Physicians. Reducing firearm injuries and deaths in the United States: a position paper from the American College of Physicians. *Ann Intern Med.* 2018;169:704-707.
4. Papenfuss M. NRA Tweets Warning to Anti-Gun Doctors: 'Stay In Your Lane'. *The Huffington Post*. November 8, 2018.
5. Everytown for Gun Safety website. Mass Shootings in the United States: 2009–2016. Available at https://everytownresearch.org/reports/mass-shootings-analysis/. Accessed January 17, 2019.
6. The American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 518: intimate partner violence. *Obstet Gynecol*. 2012;119(2 pt 1):412-417. https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Intimate-Partner-Violence.
7. Zeoli AM, McCourt A, Buggs S, et al. Analysis of the strength of legal firearms restrictions for perpetrators of domestic violence and their associations with intimate partner homicide. *Am J Epidemiol.* 2018;187:2365-2371.

MDedge™ | ObGyn

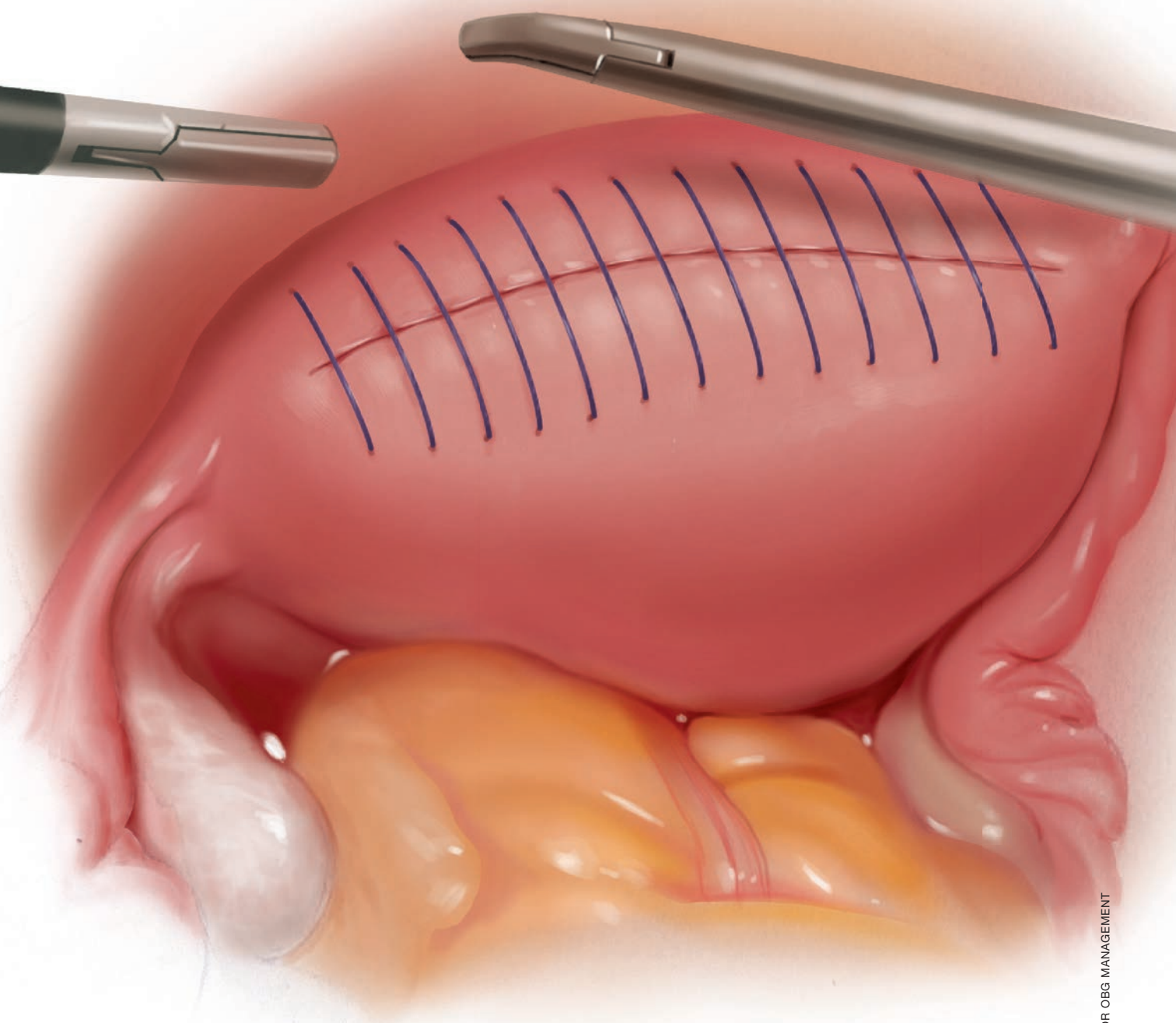
Ongoing gynecologic cancer resources for your practice

Did you read these recent news and clinical articles?

- Obesity-related cancers increasing in younger adults
- When NOT to perform a Pap test
- Nationwide implementation of MIS reduced complications and increased survival in early-stage endometrial cancer
- Soy didn't up all-cause mortality in breast cancer survivors
- Should we abandon minimally invasive surgery for cervical cancer?
- Study shows evidence of herd immunity with HPV vaccine
- The HPV vaccine is now recommended for adults aged 27–45: Counseling implications
- BMI changes in adolescence linked to later cancer risk
- Maternal health benefits of breastfeeding
- Does low-dose aspirin decrease a woman's risk of ovarian cancer?
- When is it appropriate to remove ovaries in hysterectomy?
- Addressing your patient's sexual function after cancer



Bookmark the GYNECOLOGIC CANCER page at **mdedge.com/obgyn**



Focal adenomyosis treated by wedge resection of the diseased myometrium, with subsequent closure of the remaining myometrial defect using a barbed V-Loc delayed absorbable suture in layers.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

HOW DO YOU PROCEED?

A patient with severe adenomyosis requests uterine-sparing surgery

Combined laparoscopy and, when necessary, minilaparotomy is the authors' preferred technique. It can relieve many symptoms of adenomyosis with a low complication rate, and preserve, even improve, fertility

Camran Nezhat, MD; Michelle A. Wood, DO; Megan Kennedy Burns, MD, MA; and Azadeh Nezhat, MD

CASE

A 28-year-old patient presents for evaluation and management of her chronic pelvic pain, dysmenorrhea, and menorrhagia. She previously tried ibuprofen with no pain relief. She also tried oral and long-acting reversible contraceptives but continued to be symptomatic. She underwent pelvic sonography, which demonstrated a large globular uterus with myometrial thickening and myometrial cysts with increased hypervascularity. Subsequent magnetic resonance imaging indicated a thickened junctional zone. Feeling she had exhausted medical manegement options with no significant improvement, she desired surgical treatment, but wanted to retain her future fertility. As a newlywed, she and her husband were planning on building a family so she desired to retain her uterus for potential future pregnancy.

How would you address this patient's disruptive symptoms, while affirming her long-term plans by choosing the proper intervention?

Dr. C. Nezhat is Director of the Camran Nezhat Institute, Palo Alto, California, and Founder of Worldwide Endometriosis March.

Dr. Wood is Fellow, Camran Nezhat Institute.

Dr. Burns is Fellow, Camran Nezhat Institute.

Dr. A. Nezhat is Co-Director, Center for Special Minimally Invasive and Robotic Surgery, Palo Alto, California.

The authors report no financial relationships relevant to this article.

Adenomyosis is characterized by endometrial-like glands and stroma deep within the myometrium of the uterus and generally is classified as diffuse or focal. This common, benign gynecologic condition is known to cause enlargement of the uterus secondary to stimulation of ectopic endometrial-like cells.[1-3] Although the true incidence of adenomyosis is unknown because of the difficulty of making the diagnosis, prevalence has been variously reported at 6% to 70% among reproductive-aged women.[4,5]

In this review, we first examine the clinical presentation and diagnosis of adenomyosis. We then discuss clinical indications for, and surgical techniques of, adenomyomectomy, including our preferred uterine-sparing approach for focal disease or when the patient wants to preserve fertility: laparoscopic resection without robotic assistance, aided by minilaparotomy when indicated.

Treatment evolved in a century and a half

Adenomyosis was first described more than 150 years ago; historically, hysterectomy was the mainstay of treatment.[2,6] Conservative surgical treatment for adenomyosis has been reported since the early 1950s.[6-8] Surgical treatment initially became more widespread following the introduction of wedge resection,

IN THIS ARTICLE

which allowed for partial excision of adenomyotic nodules.[9]

More recent developments in diagnostic technologies and capabilities have allowed for the emergence of additional uterine-sparing and minimally invasive surgical treatment options for adenomyosis.[3,10] Although the use of laparoscopic approaches is limited because a high level of technical skill is required to undertake these procedures, such approaches are becoming increasingly important as more and more patients seek fertility conservation.[11-13]

How does adenomyosis present?

Adenomyosis symptoms commonly consist of abnormal uterine bleeding and dysmenorrhea, affecting approximately 40% to 60% and 15% to 30% of patients with the condition, respectively.[14] These symptoms are considered nonspecific because they are also associated with other uterine abnormalities.[15] Although menorrhagia is not associated with extent of disease, dysmenorrhea is associated with both the number and depth of adenomyotic foci.[14]

Other symptoms reported with adenomyosis include chronic pelvic pain, dyspareunia, as well as infertility. Note, however, that a large percentage of patients are asymptomatic.[16,17]

On physical examination, patients commonly exhibit a diffusely enlarged, globular uterus. This finding is secondary to uniform hyperplasia and hypertrophy of the myometrium, caused by stimulation of ectopic endometrial cells.[2] A subset of patients experience significant uterine tenderness.[18] Other common findings associated with adenomyosis include uterine abnormalities, such as leiomyomata, endometriosis, and endometrial polyps.

FAST TRACK

Stimulation of ectopic endometrial cells causes uniform hyperplasia and hypertrophy of the myometrium, resulting in an enlarged uterus that often presents on physical exam

Two-pronged route to diagnosis and a differential

Histology

Adenomyosis is definitively diagnosed based on histologic findings of endometrial-like tissue within the myometrium. Historically, histologic analysis was performed on specimens following hysterectomy but, more recently, has utilized specimens obtained from hysteroscopic and laparoscopic myometrial biopsies.[19] Importantly, although hysteroscopic and laparoscopic biopsies are taken under direct visualization, there are no pathognomonic signs for adenomyosis; a diagnosis can therefore be missed if adenomyosis is not present at biopsied sites.[1] The sensitivity of random biopsy at laparoscopy has been found to be as low as 2% to as high as 56%.[20]

Imaging

Imaging can be helpful in clinical decision making and to guide the differential diagnosis. Transvaginal ultrasonography (TVUS) is often the first mode of imaging used for the investigation of abnormal uterine bleeding or pelvic pain. Diagnosis by TVUS is difficult because the modality is operator dependent and standard diagnostic criteria are lacking.[5]

The most commonly reported ultrasonographic features of adenomyosis are[21,22]:

- a globally enlarged uterus
- asymmetry
- myometrial thickening with heterogeneity
- poorly defined foci of hyperechoic regions, surrounded by hypoechoic areas that correspond to smooth-muscle hyperplasia
- myometrial cysts.

Doppler ultrasound examination in patients with adenomyosis reveals increased flow to the myometrium without evidence of large blood vessels.

3-dimensional (3-D) ultrasonography. Integration of 3-D ultrasonography has allowed for identification of the thicker junctional zone that suggests adenomyosis. In a systematic review of the accuracy of TVUS, investigators reported a pooled sensitivity and specificity for 2-dimensional ultrasonography of 83.8% and 63.9%, respectively, and a pooled sensitivity and specificity for 3-dimensional ultrasonography of 88.9% and 56.0%, respectively.[22]

Magnetic resonance imaging (MRI) is also used in the evaluation of adenomyosis. Although MRI is considered a more accurate

CONTINUED ON PAGE 32

WELCOME TO

MDedge™

A destination for the latest news, conference coverage and clinical content from over 35 specialty publications and websites.

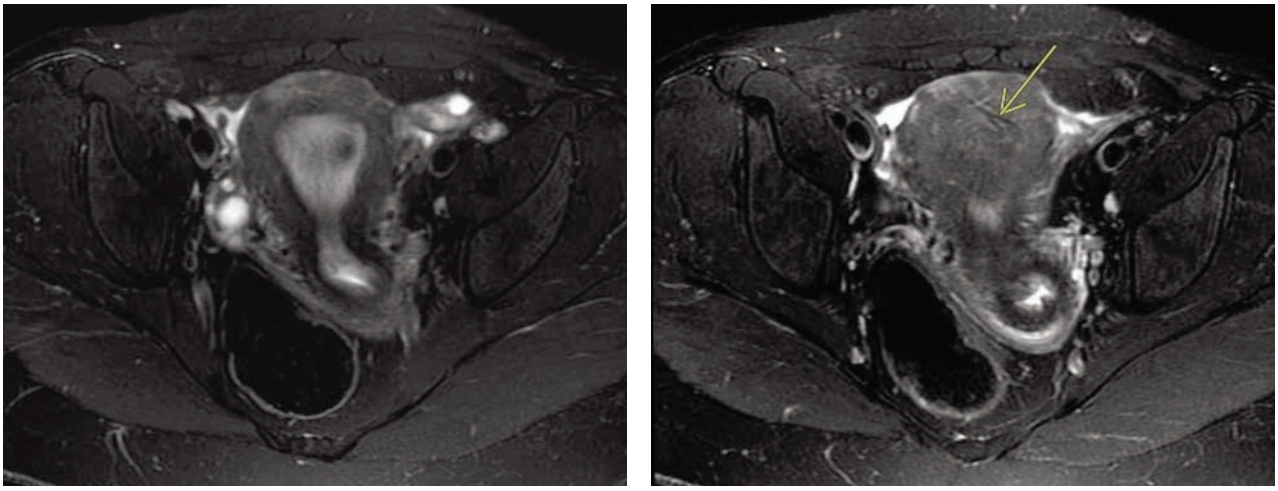
Latest news • Clinical perspectives • Podcasts
Medical education • Latest guidelines • Business of medicine
MDIQ • Lifestyle • Clinical Edge

MDedge.com

Keeping You Informed. Saving You Time.

CONTINUED FROM PAGE 30

FIGURE 1 MRI suggests adenomyosis



Left: Asymmetrical thickening of the myometrium. Right: Hyperintense foci within the uterine body.

diagnostic modality because it is not operator dependent, expense often prohibits its use in the work-up of abnormal uterine bleeding and chronic pelvic pain.[2,23]

The most commonly reported MRI findings in adenomyosis include a globular or asymmetric uterus, heterogeneity of myometrial signal intensity, and thickening of the junctional zone[24] (**FIGURE 1**). In a systematic review, researchers reported a pooled sensitivity and specificity of 77% and 89%, respectively, for the diagnosis of adenomyosis using MRI.[25]

FAST TRACK

Off-label medical management options include: oral contraceptive pills (combined or progestin only), GnRH agonists, LNG-IUDs, danazol, and aromatase inhibitors

Approaches to treatment

Medical management

No medical therapies or guidelines specific to the treatment of adenomyosis exist.[9] Often, nonsteroidal anti-inflammatory drugs (NSAIDs) are employed to combat cramping and pain associated with increased prostaglandin levels.[26] A systematic review found that NSAIDs are significantly better at treating dysmenorrhea than placebo alone.[26]

Moreover, adenomyosis is an estrogen-dependent disease; consequently, many medical treatments are targeted at suppressing the hypothalamic–pituitary–ovarian axis and inducing endometrial atrophy. Medications commonly used (off-label) for this effect include combined or progestin-only oral contraceptive pills, gonadotropin-releasing hormone (GnRH) agonists, levonorgestrel-releasing intrauterine devices, danazol, and aromatase inhibitors.

Use of a GnRH agonist, such as leuprolide, is limited to a short course (<6 months) because menopausal-like symptoms, such as hot flashes, vaginal atrophy, and loss of bone-mineral density, can develop.[16] Symptoms of adenomyosis often return upon cessation of hormonal treatment.[1]

Novel therapies are under investigation, including GnRH antagonists, selective progesterone-receptor modulators, and antiplatelet therapy.[27]

Although there are few data showing the effectiveness of medical therapy on adenomyosis-specific outcomes, medications are particularly useful in patients who are poor surgical candidates or who may prefer not to undergo surgery. Furthermore, medical therapy has considerable use in conjunction with surgical intervention; a prospective observational study showed that women who underwent GnRH agonist treatment following surgery had significantly greater improvement of their dysmenorrhea and menorrhagia, compared with those who underwent surgery only.[28] In addition, preoperative administration of a GnRH agonist or

danazol several months prior to surgery has been shown to reduce uterine vascularity and, thus, blood loss at surgery.[29,30]

Surgery

The objective of surgical management is to ameliorate symptoms in a conservative manner, by excision or cytoreduction of adenomyotic lesions, while preserving, even improving, fertility.[3,11,31] The choice of procedure depends, ultimately, on the location and extent of disease, the patient's desire for uterine preservation and fertility, and surgical skill.[3]

Historically, hysterectomy was used to treat adenomyosis; for patients declining fertility preservation, hysterectomy remains the definitive treatment. Since the early 1950s, several techniques for laparotomic reduction have been developed. Surgeries that achieve partial reduction include:

Wedge resection of the uterine wall entails removal of the seromuscular layer at the identified location of adenomyotic tissue, with subsequent repair of the remaining muscular and serosal layers surrounding the wound.[3,32] Because adenomyotic tissue can remain on either side of the incision in wedge resection, clinical improvement in symptoms of dysmenorrhea and menorrhagia are modest, and recurrence is possible.[7]

Modified reduction surgery. Modifications of reduction surgery include slicing adenomyotic tissue using microsurgery and partial excision.[33]

Transverse-H incision of the uterine wall involves a transverse incision on the uterine fundus, separating serosa and myometrium, followed by removal of diseased tissue using an electrosurgical scalpel or scissors. Tensionless suturing is used to close the myometrial layers in 1 or 2 layers to establish hemostasis and close the defect; serosal flaps are closed with subserosal interrupted sutures.[34] Data show that, following surgery with this technique, 21.4% to 38.7% of patients who attempt conception achieve clinical pregnancy.[7]

Complete, conservative resection in cases of diffuse and focal adenomyosis is possible using the triple-flap method, in which total resection is achieved by removing diseased myometrium until healthy, soft tissue—with normal texture, color, and vascularity—is reached.[2] Repair with this technique reduces the risk of uterine rupture by reconstructing the uterine wall using a muscle flap prepared by metroplasty.[7] In a study of 64 women who underwent triple-flap resection, a clinical pregnancy rate of 74% and a live birth rate of 52% were reported.[7]

Minimally invasive approaches. Although several techniques have been developed for focal excision of adenomyosis by laparotomy,[7] the trend has been toward minimally invasive surgery, which reduces estimated blood loss, decreases length of stay, and reduces adhesion formation—all without a statistically significant difference in long-term clinical outcomes, compared to other techniques.[35-39] Furthermore, enhanced visualization of pelvic organs provided by laparoscopy is vital in the case of adenomyosis.[3,31]

How our group approaches surgical management. A challenge in laparoscopic surgery of adenomyosis is extraction of an extensive amount of diseased tissue. In 1994, our group described the use of simultaneous operative laparoscopy and minilaparotomy technique as an effective and safe

Key practice points in managing adenomyosis

- Adenomyosis is common and benign, but remains underdiagnosed because of a nonspecific clinical presentation and lack of standardized diagnostic criteria.
- Adenomyosis can cause significant associated morbidity: dysmenorrhea, heavy menstrual bleeding, chronic pelvic pain, and infertility.
- High clinical suspicion warrants evaluation by imaging.
- Medical management is largely aimed at ameliorating symptoms.
- A patient who does not respond to medical treatment or does not desire pregnancy has a variety of surgical options; the extent of disease and the patient's wish for uterine preservation guide the selection of surgical technique.
- Hysterectomy is the definitive treatment but, in patients who want to avoid radical resection, techniques developed for laparotomy are available, to allow conservative resection using laparoscopy.
- Ideally, surgery is performed using a combined laparoscopy and minilaparotomy approach, after appropriate imaging.

FAST TRACK

After appropriate imaging, ideal surgical management includes a combined laparoscopy and minilaparotomy approach

Pathophysiology of adenomyosis

How adenomyosis originates is not fully understood. Several theories have been proposed, however (including, more prominently, the first 2 below):

Invasion theory. The endometrial basalis layer invaginates and invades the myometrium[1,2] (**FIGURE**); the etiology of invagination remains unknown.

Reaction theory. Myometrial weakness or dysfunction, brought on by trauma from previous uterine surgery or pregnancy, could predispose uterine musculature to deep invasion.[3]

Metaplasia theory. Adenomyosis is a result of metaplasia of pluripotent Müllerian rests.

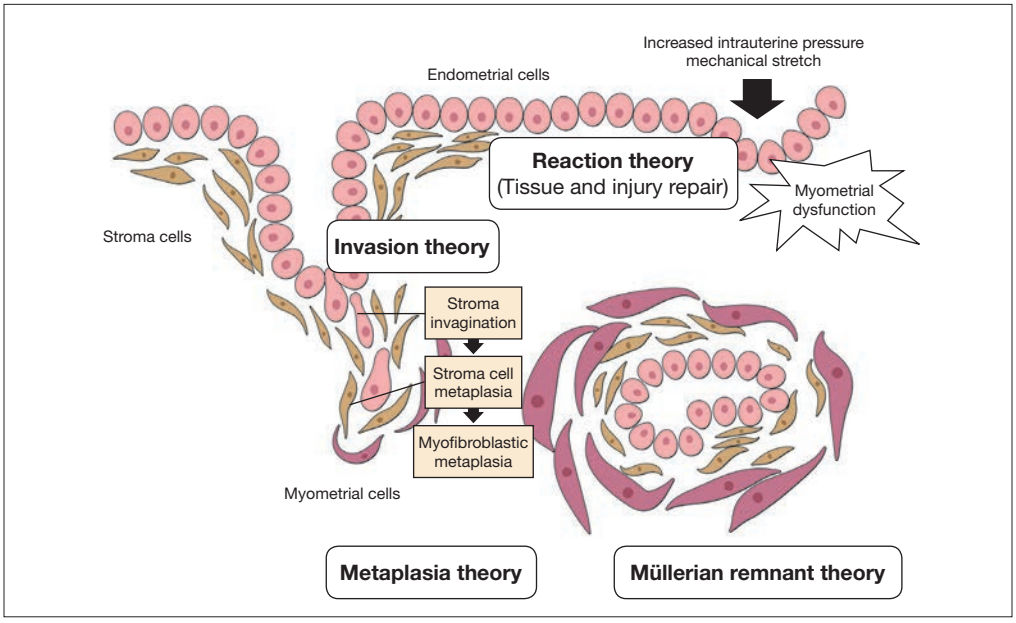
Müllerian remnant theory. Related to the Müllerian metaplasia theory, adenomyosis is formed de novo from 1) adult stem cells located in the endometrial basalis that is involved in the cyclic regeneration of the endometrium[4-6] or 2) adult stem cells displaced from bone marrow.[7,8]

Once adenomyosis is established, it is thought to progress by epithelial–mesenchymal transition,[2] a process by which epithelial cells become highly motile mesenchymal cells that are capable of migration and invasion, due to loss of cell–cell adhesion properties.[9]

FAST TRACK

The invasion theory, which asserts that the endometrial basalis layer invades the myometrium, is only one of several proposed mechanisms of adenomyosis development

FIGURE Competing theories of adenomyosis pathogenesis



References

1. Struble J, Reid S, Bedaiwy MA. Adenomyosis: a clinical review of a challenging gynecologic condition. *J Minim Invasive Gynecol.* 2016; 23:164-185.
2. García-Solares J, Donnez J, Donnez O, et al. Pathogenesis of uterine adenomyosis: invagination or metaplasia? *Fertil Steril.* 2018;109:371-379.
3. Ferenczy A. Pathophysiology of adenomyosis. *Hum Reprod Update.* 1998;4:312-322.
4. Gargett CE. Uterine stem cells: what is the evidence? *Hum Reprod Update.* 2007;13:87-101.
5. Chan RW, Schwab KE, Gargett CE. Clonogenicity of human endometrial epithelial and stromal cells. *Biol Reprod.* 2004;70:1738-1750.
6. Schwab KE, Chan RWS, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. *Fertil Steril.* 2005;84(Suppl 2):1124-1130.
7. Sasson IE, Taylor HS. Stem cells and the pathogenesis of endometriosis. *Ann N Y Acad Sci.* 2008;1127:106-115.
8. Du H, Taylor HS. Stem cells and female reproduction. *Reprod Sci.* 2009;16:126-139.
9. Acloque H, Adams MS, Fishwick K, et al. Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease. *J Clin Invest.* 2009;119:1438-1449.

CONTINUED ON PAGE 36

Ob.Gyn. News®

STAY TUNED

for meeting coverage from the Pelvic Anatomy and Gynecologic Surgery Symposium

DON'T MISS

our exclusive columns

> Drugs, Pregnancy, & Lactation

> Gynecologic Oncology Consult

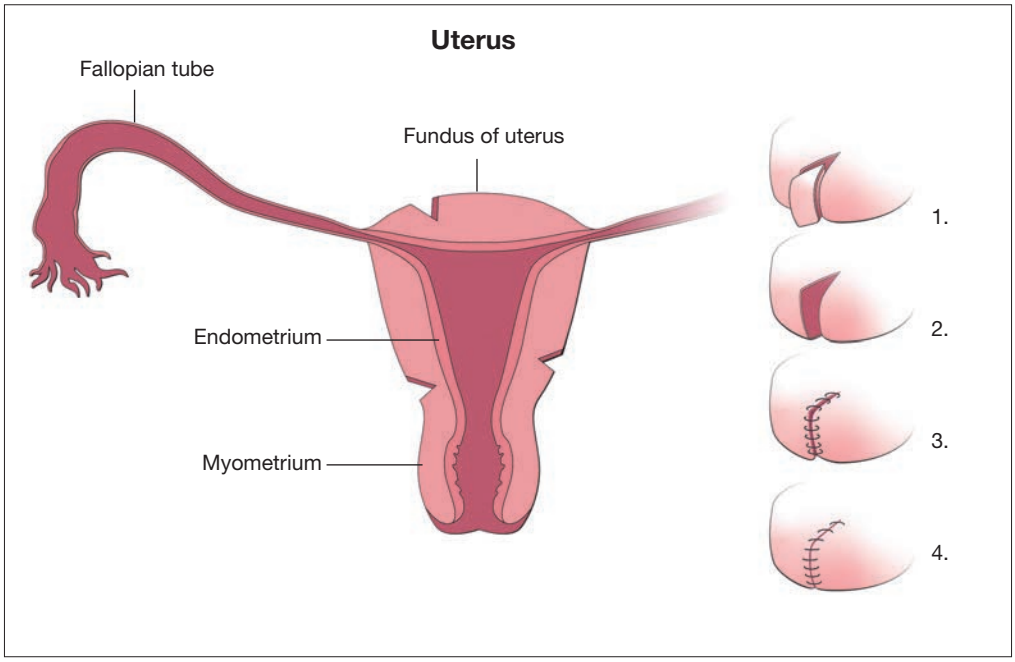
> Master Class

GET BREAKING NEWS

at **mdedge.com/obgyn**

CONTINUED FROM PAGE 34

FIGURE 2 Wedge resection of focal adenomyosis



The authors' preferred uterine-sparing surgical approach to focal adenomyosis, or when a patient wants to preserve fertility.

FAST TRACK

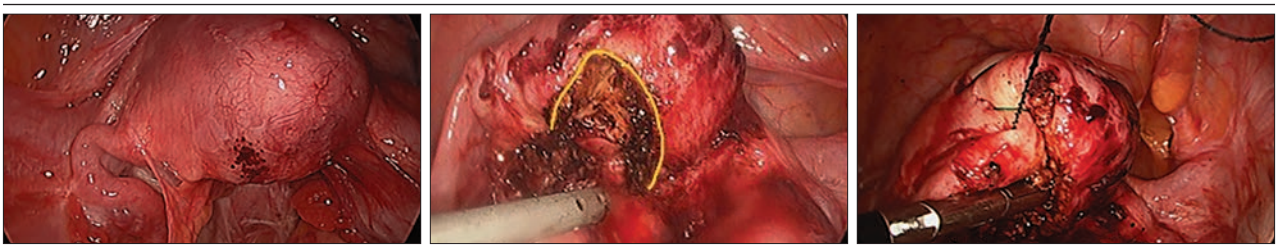
Our preferred approach to provide symptom relief and to preserve fertility is laparoscopic wedge resection without robotic assistance (with minilaparotomy for larger adenomyomas)

alternative to laparotomy in the treatment of myomectomy[6]; the surgical principles of that approach are applied to adenomyomectomy. The technique involves treatment of pelvic pathology with laparoscopy, removal of tissue through the minilaparotomy incision, and repair of the uterine wall defect in layers.

In 57 women who underwent this procedure, the mean operative time was 127 minutes; average estimated blood loss was 267 mL.[40] Overall, laparoscopy with minilaparotomy was found to be a less technically difficult technique for laparoscopic myomectomy; allowed better closure of the uterine defect; and might have required less time to perform.[3]

We therefore advocate laparoscopic wedge resection without robotic assistance, aided by minilaparotomy when necessary for safe removal of larger adenomyomas, as the preferred uterine-sparing surgical approach for focal adenomyosis or when the patient wants to preserve fertility (**FIGURE 2**). We think that this technique allows focal adenomyosis to be treated by wedge resection of the diseased myometrium, with subsequent closure of the remaining myometrial defect using a barbed V-Loc (Medtronic, Minneapolis, Minnesota) delayed absorbable suture in layers (**FIGURE 3**). Minilaparotomy can be

FIGURE 3 Surgical wedge resection and closure



utilized when indicated to aid removal of the resected myometrial specimen.

In our extensive experience, we have found that this technique provides significant relief of symptoms and improvements in fertility outcomes while minimizing surgical morbidity.

CASE Resolved

The patient underwent successful wedge resection of her adenomyosis by laparoscopy. She experienced nearly complete resolution of her symptoms of dysmenorrhea, menorrhagia, and pelvic pain. She retained good uterine integrity. Three years later, she and her husband became parents when she delivered their first child by cesarean delivery at full term. After she completed childbearing, she ultimately opted for minimally invasive hysterectomy. ●

The authors would like to acknowledge Mailinh Vu, MD, Fellow at Camran Nezhat Institute, for reviewing and editing this article.

References

1. Garcia L, Isaacson K. Adenomyosis: review of the literature. *J Minim Invasive Gynecol*. 2011;18:428-437.
2. Nezhat C, Nezhat F, Nezhat C, eds. *Nezhat's Video-Assisted and Robotic-Assisted Laparoscopy and Hysteroscopy*. 4th ed. Cambridge, UK: Cambridge University Press; 2013.
3. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. *Fertil Steril*. 2018;109:406-417.
4. Azziz R. Adenomyosis: current perspectives. *Obstet Gynecol Clin North Am*. 1989;16:221-235.
5. Struble J, Reid S, Bedaiwy MA. Adenomyosis: A clinical review of a challenging gynecologic condition. *J Minim Invasive Gynecol*. 2016;23:164-185.
6. Rokitansky C. Ueber Uterusdrsen-Neubildung in Uterus- und Ovarial-Sarcomen. Gesellschaft der Ärzte in Wien. 1860;16:1-4.
7. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. *Fertil Steril*. 2018;109:406-417.
8. Van Praagh I. Conservative surgical treatment for adenomyosis uteri in young women: local excision and metroplasty. *Can Med Assoc J*. 1965;93:1174-1175.
9. Donnez J, Donnez O, Dolmans MM. Introduction: Uterine adenomyosis, another enigmatic disease of our time. *Fertil Steril*. 2018;109:369-370.
10. Nishida M, Takano K, Arai Y, et al. Conservative surgical management for diffuse uterine adenomyosis. *Fertil Steril*. 2010;94:715-719.
11. Abbott JA. Adenomyosis and abnormal uterine bleeding (AUB-A)—Pathogenesis, diagnosis, and management. *Best Pract Res Clin Obstet Gynaecol*. 2017;40:68-81.
12. Matalliotakis IM, Katsikis IK, Panidis DK. Adenomyosis: what is the impact on fertility? *Curr Opin Obstet Gynecol*. 2005;17:261-264.
13. Devlieger R, D'Hooghe T, Timmerman D. Uterine adenomyosis in the infertility clinic. *Hum Reprod Update*. 2003;9:139-147.
14. Levgur M, Abadi MA, Tucker A. Adenomyosis: symptoms, histology, and pregnancy terminations. *Obstet Gynecol*. 2000;95:688-691.
15. Weiss G, Maseelall P, Schott LL, et al. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). *Fertil Steril*. 2009;91:201-206.
16. Huang F, Kung FT, Chang SY, et al. Effects of short-course buserelin therapy on adenomyosis. A report of two cases. *J Reprod Med*. 1999;44:741-744.
17. Benson RC, Sneeden VD. Adenomyosis: a reappraisal of symptomatology. *Am J Obstet Gynecol*. 1958;76:1044-1061.
18. Shrestha A, Sedai LB. Understanding clinical features of adenomyosis: a case control study. *Nepal Med Coll J*. 2012;14:176-179.
19. Fernández C, Ricci P, Fernández E. Adenomyosis visualized during hysteroscopy. *J Minim Invasive Gynecol*. 2007;14:555-556.
20. Brosens JJ, Barker FG. The role of myometrial needle biopsies in the diagnosis of adenomyosis. *Fertil Steril*. 1995;63:1347-1349.
21. Van den Bosch T, Van Schoubroeck D. Ultrasound diagnosis of endometriosis and adenomyosis: state of the art. *Best Pract Res Clin Obstet Gynaecol. 2018;51:16-24.*
22. Andres MP, Borrelli GM, Ribeiro J, et al. Transvaginal ultrasound for the diagnosis of adenomyosis: systematic review and meta-analysis. *J Minim Invasive Gynecol*. 2018;25:257-264.
23. Bazot M, Cortez A, Darai E, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. *Hum Reprod*. 2001;16:2427-2433.
24. Bragheto AM, Caserta N, Bahamondes L, et al. Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. *Contraception*. 2007;76:195-199.
25. Champaneria R, Abedin P, Daniels J, et al. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. *Acta Obstet Gynecol Scand*. 2010; 89:1374-1384.
26. Marjoribanks J, Proctor M, Farquhar C, et al. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*. 2010;(1):CD001751.
27. Vannuccini S, Luisi S, Tosti C, et al. Role of medical therapy in the management of uterine adenomyosis. *Fertil Steril*. 2018;109:398-405.
28. Wang PH, Liu WM, Fuh JL, et al. Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. *Fertil Steril*. 2009;92:876-885.
29. Wood C, Maher P, Woods R. Laparoscopic surgical techniques for endometriosis and adenomyosis. *Diagn Ther Endosc*. 2000;6:153-168.
30. Wang CJ, Yuen LT, Chang SD, et al. Use of laparoscopic cytoreductive surgery to treat infertile women with localized adenomyosis. *Fertil Steril*. 2006;86:462.e5-e8.
31. Nezhat C, Hajhosseini B, King LP. Robotic-assisted laparoscopic treatment of bowel, bladder, and ureteral endometriosis. *JSLS*. 2011;15:387-392.
32. Sun A, Luo M, Wang W, et al. Characteristics and efficacy of modified adenomyomectomy in the treatment of uterine adenomyoma. *Chin Med J*. 2011;124:1322-1326.
33. Fedele L, Bianchi S, Zanotti F, et al. Surgery: Fertility after conservative surgery for adenomyomas. *Hum Reprod*. 1993;8:1708-1710.
34. Fujishita A, Masuzaki H, Khan KN, et al. Modified reduction surgery for adenomyosis. A preliminary report of the transverse H incision technique. *Gynecol Obstet Invest*.

CONTINUED ON PAGE 49

BREAK THIS PRACTICE HABIT

Uterine aspiration: From OR to office

Compared with uterine aspiration in the OR, an office-based procedure is as safe, less expensive, and more patient centered—all reasons to make it the standard for surgical management of early pregnancy failure

Lauren Thaxton, MD, MBA, and Bri Tristan, MD

IN THIS ARTICLE

CASE Patient with early pregnancy failure opts for surgical management

A 36-year-old woman (G3P2) at 9 weeks from her last menstrual period presents for an initial obstetric examination. On transvaginal ultrasound, her ObGyn notes an embryo measuring 9 weeks without cardiac activity. The ObGyn informs her of the early pregnancy failure diagnosis and offers bereavement support, and then reviews the available options: expectant management with follow-up in 2 weeks, medical management with mifepristone and misoprostol, and surgical management with a dilation and curettage (D&C). The patient is interested in expedited treatment and thus selects D&C, and the staff books the next available operating room (OR) slot for her the subsequent week. Over the weekend, the patient calls to report heavy bleeding and passage of clots, and the ObGyn's practice partner takes her to the OR for a D&C for incomplete abortion.

Early pregnancy failure occurs in about 1 in 5 pregnancies. Treatment options include expectant, medical, or surgical management. Surgical management is classically offered in the OR via D&C. With the advent of manual vacuum aspiration (MVA) using a 60-mL handheld syringe aspirator, office-based treatment of pregnancy failure has become more widely available.

In this article we make the case for why, in appropriate clinical situations, office-based uterine aspiration, compared with uterine aspiration in the OR, should be the standard for surgical management of early pregnancy failure, for these reasons:

1. equivalent safety profile
2. reduced costs, and
3. patient-centered characteristics.

1 Office-based procedures are safe

Suction curettage is one of the most common surgical procedures for a woman to undergo

Dr. Thaxton is Assistant Professor, Department of Women's Health, University of Texas at Austin.

Dr. Tristan is Assistant Professor and Residency Program Director, Department of Women's Health, University of Texas at Austin.

The authors report no financial relationships relevant to this article.

Instant Poll

Do you agree that the standard location for uterine aspiration should be in the office?

- **Yes, in appropriate clinical situations**
- **No**

Tell us at **rbarbieri@mdedge.com**
Please include your name and city and state.

CONTINUED ON PAGE 40

CONTINUED FROM PAGE 38

during her lifetime, and it has an excellent safety profile. Authors of a recent systematic review found that major surgical complications, including transfusion and uterine perforation requiring repair, occurred in less than 0.1% of all uterine aspiration procedures.[1] Importantly, this complication rate did not differ by inpatient or outpatient site of procedure.

Anesthesia-related complications at the time of aspiration also are extremely rare, and they are less likely to occur in the office setting than in surgical centers or hospital-based clinics (<0.2% and <0.5%, respectively).[1] This may be a result of the types of anesthesia offered at varying locations, given that local analgesia or moderate sedation is likely used in office-based procedures while deep sedation or general anesthesia may be employed at other practice locations.

Studies specifically designed to determine the safety of suction aspiration by practice location have yielded similar results. Researchers who conducted a systematic review comparing the safety of procedures done at ambulatory surgical centers with office-based procedures found no difference in safety between procedures performed in these 2 settings.[2] These findings were confirmed by results from a large retrospective cohort study that reviewed more than 50,000 aspiration procedures performed in ambulatory surgical centers versus private offices.[3] In that study, only 0.32% of women had any major adverse event, and there were no statistically significant differences in complication rates between settings.[3]

Complication rates based on procedure type are similar for MVA and electric suction aspiration. Early studies revealed no difference in the need for reaspiration or other complications for MVA compared with electric suction.[4] This was later confirmed by a systematic review that found no significant differences in safety by type of suction overall, and a possible trend toward fewer uterine perforations with MVA.[5] When procedures were assessed by gestational age, additional trends toward the safety of MVA emerged. For example, in procedures performed at less than 50 days' gestational age, estimated blood loss and severe pain occurred less commonly during procedures performed using MVA.[5]

FAST TRACK

Major surgical complications occurred in less than 0.1% of all uterine aspiration procedures, and the rate did not differ by inpatient or outpatient site of procedure

2 Office-based procedures are less expensive

There has been a trend in recent decades to obtain cost savings by moving appropriately selected gynecologic procedures from the operative suite to the outpatient setting. Because of MVA's minimal up-front and ongoing costs, office-based suction aspiration is one of the most cost-effective procedures performed in the outpatient setting.

Dalton and colleagues, for example, demonstrated that in women diagnosed with early pregnancy failure, suction curettage is 50% less expensive when performed in the office as compared to in the operating suite.[6] Likewise, in a cohort of patients who presented to the emergency department with an incomplete abortion, Blumenthal and colleagues showed a 41% procedural cost reduction by offering D&C in the outpatient setting instead of the OR.[7] Waiting times and mean procedure times also were reduced by nearly half.

Recent studies have broadened cost analyses beyond the comparison of inpatient versus outpatient procedures. A multicenter trial of women with first-trimester pregnancy failure compared the costs of medication management with those of surgical procedures; as expected, the cost of D&C in the OR was significantly more expensive than medication management.[8] However, MVA in the office was less expensive than medication management, due largely to the increased cost of managing medication failures.

In addition, a recent, well-designed decision model study demonstrated that offering women with early pregnancy failure a greater array of management options decreases costs.[9] The study compared the costs when women were offered the most common options, expectant management or uterine evacuation in the OR, versus the costs when additional options were also offered. When options were expanded to include medication management and MVA

CONTINUED ON PAGE 42

THE CURE FOR INFORMATION OVERLOAD

ALLMEDx.com

Introducing a new and better search engine for physicians!

- Unique search algorithm with no consumer links
- Essential and refined physician-based content
- Less is more results saves you time!

What physicians are saying about ALLMEDx.com

"ALLMEDx.com got me where I wanted to go faster and more precisely than other search sites—and that's key!"

"ALLMEDx.com eliminates the irrelevant without effort on my part. That's useful!"

"ALLMEDx.com separates the wheat from the chaff, saving me time and effort"

*Go to **ALLMEDx.com** and compare!*

CONTINUED FROM PAGE 40

in the office, costs decreased by nearly 20% overall.[9]

3 Office-based procedures are more patient centered

The benefits of surgical management of an early pregnancy failure include very high success rates (98%) and convenient timing. Among women who elect surgical management, a desire to expedite the process in a predictable fashion is a common factor in their decision.[10,11] It is unsurprising then that 68% of patients will select an office-based procedure if they do not perceive that the clinician has a setting preference.[6]

When surgical management is performed in the OR, scheduling delays are common. Such delays can be clinically important: Women progressing to a miscarriage while awaiting surgical treatment may be at risk for urgent, unplanned interval procedures for incomplete abortion, and they may be dissatisfied with the inability to access the desired management. While women are highly satisfied after treatment for early pregnancy failure in general,[6] OR treatment can cause dissatisfaction because patients miss more work days or need assistance at home.[12] In a cross-sectional study, patients who elected office-based aspiration reported less delay to treatment (less than 2 hours) compared with women who elected OR procedures (more than 12 hours), and shorter time to procedure initiation was a satisfier.[13]

Women also note fear of the hospital setting and general anesthesia, and they tend to see hospital-based services as more invasive.[11] Clinicians can offer anesthesia in the outpatient setting with nonsteroidal anti-inflammatory medications and a paracervical block, oral sedation with an anxiolytic, or in some cases intravenous (IV) sedation with conscious sedation.

FAST TRACK

Very high success rates and convenient timing are 2 benefits of surgical management of an early pregnancy failure

Our process for office-based uterine aspiration

We follow the step-by-step process outlined below for performing office-based uterine aspiration. Clinicians should review their clinic's protocols prior to implementing such a plan.

Review the patient history and pregnancy dating. Patients with serious medical conditions, such as history of postabortion hemorrhage or a bleeding disorder, may not be appropriate candidates for an office-based procedure. We perform bedside ultrasonography to confirm pregnancy dating and diagnosis of pregnancy failure.

Review consent for the procedure and sedation. Risks of office-based uterine aspiration are the same as those for D&C: bleeding, uterine perforation, and failure to fully evacuate the uterus. Benefits include rapid, safe evacuation of the pregnancy. Alternative treatments include expectant or medical management.

For pain management, we start by discussing expectations with the patient. Providing general anesthesia in the outpatient setting is not safe; many women are satisfied, however, with local anesthesia with or without sedation.

Local anesthesia may be given using a paracervical block with 2 mL of 1% lidocaine at the tenaculum site followed by 18 mL divided between the 4 and 8 o'clock positions. In our practice, we are trained providers of conscious sedation, so additionally we offer IV fentanyl 100 µg and IV midazolam 2 mg given prior to the procedure.

Provide antibiotic prophylaxis. The American College of Obstetricians and Gynecologists and the Society for Family Planning recommend doxycycline 200 mg orally as a preoperative prophylaxis for office-based uterine aspiration.[14,15] Metronidazole is an acceptable alternative for patients who have medication allergies.

Prepare the surgical field. To complete this procedure, you will need the following equipment:

- one MVA kit that includes an aspirator, curettes, and dilators (**FIGURE,** page 44)
- 20 mL 1% lidocaine, divided into two 10-mL syringes with a 22-gauge 3.5-inch spinal needle

CONTINUED ON PAGE 44

?????

MD-IQ

The Medical Intelligence Quiz

Challenge Yourself, Build Your Knowledge

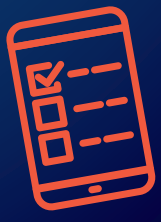
Test your knowledge with free 5-question quizzes from MDedge ObGyn!

See how your scores stack up against your peers

Receive a new quiz every Monday straight to your inbox

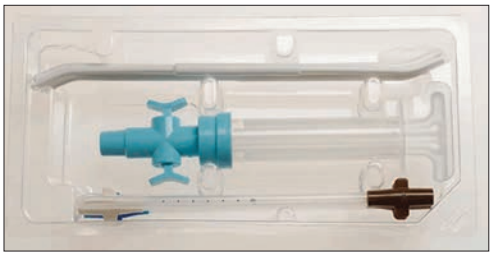
Get tested on obstetrics, gynecology, menopause, clinical guidelines, cancer, and more!

www.mdedge.com/obgyn/md-iq



CONTINUED FROM PAGE 42

FIGURE Manual vacuum evacuation kit contains syringe aspirator, curettes, and dilators



Used with permission of HPSRx Enterprises, Inc.

- speculum
- cervical antiseptic prep
- single-tooth tenaculum
- ring forceps.

Perform the MVA procedure. A full description of how to perform the MVA procedure using the Ipas MVA Plus Aspirator device is available online at http://provideaccess.org/wp-content/uploads/2012/09/4Performing-MVA-Using-the-Ipas-MVA-Plus.pdf.

A good option for many women

A D&C in the OR remains an appropriate option for patients who are clinically unstable due to heavy vaginal bleeding. With highly sensitive home urine pregnancy tests, pregnancies often are diagnosed before clinically apparent miscarriage. In fact, many such patients are diagnosed with pregnancy failure in the office, as was our patient in the case scenario. For such women, office-based management of early pregnancy failure is preferred because it is safe, cost-effective, and patient centered. ●

FAST TRACK

A D&C in the OR remains an appropriate option for patients who are clinically unstable due to heavy vaginal bleeding

References

1. White K, Carroll E, Grossman D. Complications from first-trimester aspiration abortion: a systematic review of the literature. *Contraception.* 2015;92:422-438.
2. Berglas NF, Battistelli MF, Nicholson WK, et al. The effect of facility characteristics on patient safety, patient experience, and service availability for procedures in non-hospital-affiliated outpatient settings: a systematic review. *PloS One.* 2018;13:e0190975.
3. Roberts SC, Upadhyay UD, Liu G, et al. Association of facility type with procedural-related morbidities and adverse events among patients undergoing induced abortions. *JAMA.* 2018;319:2497-2506.
4. Goldberg AB, Dean G, Kang MS, et al. Manual versus electric vacuum aspiration for early first-trimester abortion: a controlled study of complication rates. *Obstet Gynecol.* 2004;103:101-107.
5. Wen J, Cai QY, Deng F, et al. Manual versus electric vacuum aspiration for first-trimester abortion: a systematic review. *BJOG.* 2008;115:5-13.
6. Dalton VK, Harris L, Weisman CS, et al. Patient preferences, satisfaction, and resource use in office evacuation of early pregnancy failure. *Obstet Gynecol.* 2006;108:103-110.
7. Blumenthal PD, Remsburg RE. A time and cost analysis of the management of incomplete abortion with manual vacuum aspiration. *Int J Gynaecol Obstet.* 1994;45:261-267.
8. Rausch M, Lorch S, Chung K, et al. A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss. *Fertil Steril.* 2012;97:355-360.
9. Dalton VK, Liang A, Hutton DW, et al. Beyond usual care: the economic consequences of expanding treatment options in early pregnancy loss. *Am J Obstet Gynecol.* 2015;212:177.e1-6.
10. Schreiber CA, Chavez V, Whittaker PG, et al. Treatment decisions at the time of miscarriage diagnosis. *Obstet Gynecol.* 2016;128:1347-1356.
11. Smith LF, Frost J, Levitas R, et al. Women's experiences of three early miscarriage management options: a qualitative study. *Br J Gen Pract.* 2006;56:198-205.
12. Edwards S, Tureck R, Fredrick M, et al. Patient acceptability of manual versus electric vacuum aspiration for early pregnancy loss. *J Womens Health (Larchmt).* 2007;16:1429-1436.
13. Dodge LE, Hofler LG, Hacker MR, et al. Patient satisfaction and wait times following outpatient manual vacuum aspiration compared to electric vacuum aspiration in the operating room: a cross-sectional study. *Contracept Reprod Med.* 2017;2:18.
14. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 195: Prevention of infection after gynecologic procedures. *Obstet Gynecol.* 2018;131:e172-e189.
15. Achilles SL, Reeves MF; Society of Family Planning. Prevention of infection after induced abortion. *Contraception.* 2011;837:295–309.

The "Break This Practice Habit" series is spearheaded by Dr. Lauren Demosthenes, who makes overarching high value cost decisions in her role as Medical Director of High Value Care and Innovation, Department of ObGyn at Greenville Health System in Greenville, South Carolina. Watch for quarterly case presentations of low value, low evidence practices that should be questioned in current day, followed by reasons why that practice should be abandoned. If you would like to contribute to this series, please submit your query to Dr. Demosthenes at ldemosthenes@mdedge.com.

PHOTO: SHUTTERSTOCK

Woman loses hands and feet after cystectomy: $109M award

On November 1, a 45-year-old woman underwent laparoscopic excision of a benign ovarian cyst performed by a minimally invasive gynecologic (MIG) surgeon. After surgery, the patient's blood pressure (BP) declined. She was given fluids, but her BP remained low. The next day, she became incoherent and her BP could not be stabilized. Twenty-seven hours after surgery, the 5-cm umbilical incision opened while the patient was attempting to stand up from the commode. A large amount of bloody discharge drained.

At 11:00 PM that day, her BP was so low that it could not be measured, and septic shock was suspected. She was transferred to the intensive care unit (ICU), but soon went into organ failure. ICU physicians suggested that she have an abdominal computed tomography (CT) scan but she had to be stabilized before transport; they administered vasopressors.

At 4:30 PM the next day, the surgeon called for a trauma surgery consult. The trauma surgeon immediately ordered exploratory surgery and cancelled the use of vasopressors. During surgery, he found a separation in her small intestine leading to the development of necrotizing fasciitis. He resected the injured intestine and areas affected by the bacteria, including abdominal muscles and wall.

The patient remained unconscious from the time of the exploratory operation until the end of January. She required additional surgeries to control the bacteria as well as amputation of both hands above the wrists and both feet above the ankles due to gangrene. Because she no longer had an abdominal wall, a skin sac was created to hold her intestines outside of her body. When a fistula developed, a colostomy was performed.

She went to a Maryland hospital for rehab, where she learned to walk with prosthetic feet and to use her prosthetic hands. Currently, she has constant abdominal pain, can walk a short distance, and uses a wheelchair. She requires 24/7 assistance for everyday tasks. She can no longer work and is on disability.

PATIENT'S CLAIM: The patient sued the university health system that employed the MIG surgeon. During the cystectomy, he almost completely transected her small intestine, but did not find the injury during surgery. This allowed bacteria to enter the abdominal cavity, causing sepsis and necrotizing fasciitis. The trauma surgeon referred to the injury as an enterotomy, not a tear.

During the procedure, the surgeon used ADEPT, a solution to prevent the formation of adhesions. The patient's ObGyn expert concluded that ADEPT created an environment that allowed the necrotizing fasciitis to flourish.

The ICU physicians concluded that the patient was stable enough to be transported for a CT scan, but the surgeon repeatedly delayed the procedure and did not call for a surgical consult until 12 hours later. Had the CT scan or exploratory surgery occurred earlier, the diagnosis would have been discovered, and the bacteria would have been prevented from spreading. She would not have required extensive doses of vasopressors, which increase BP by cutting off blood circulation to the 4 extremities. In this case, use of vasopressors led to gangrene and the subsequent amputations.

DEFENDANTS' DEFENSE: The defendants denied all allegations. The expert witness for the defense opined that the surgeon had only nicked the intestine and that the main injury was a tear that had occurred on its own. The defense also claimed that the surgeon did not call for a CT scan because it would not have shown the source of the patient's condition.

VERDICT: After 2 trials ended with hung juries, a $109 million Florida verdict was returned against the university health system. Under Florida's sovereign immunity statute, the patient must seek recovery of all but $100,000 of the award through the Florida legislature in a separate claims bill.

This case, and those on page 46, were selected by the editors of OBG MANAGEMENT *from* Medical Malpractice Verdicts, Settlements, & Experts, *with permission of the editor, Lewis Laska (www.verdictslaska.com). The information available to the editors about the cases presented here is sometimes incomplete. Moreover, the cases may or may not have merit. Nevertheless, these cases represent the types of clinical situations that typically result in litigation and are meant to illustrate nationwide variation in jury verdicts and awards.*

CONTINUED ON PAGE 46

CONTINUED FROM PAGE 45

Child has hypoxic brain injury: $7.75M settlement

At 41 weeks' gestation, a mother presented to the emergency department (ED) for delivery after an unremarkable pregnancy. During the last 90 minutes of labor, fetal heart-rate (FHR) monitoring showed nonreassuring findings. After a vaginal delivery, the infant was found to have a hypoxic brain injury.

PARENTS' CLAIM: Even though nonreassuring FHR monitoring findings occurred, the physicians did not offer cesarean delivery (CD). The pediatrician and ED physician were negligent in failing to provide proper neonatal resuscitation and in recognizing a problem with the infants' intubation. The delay in delivery and poor resuscitation procedure caused the child's injury.

DEFENDANTS' DEFENSE: All allegations were denied. There was no deviation from the standard of care.

VERDICT: A $7.75 million Massachusetts settlement was reached.

Kidney failed after hysterectomy

A 46-year-old woman underwent a hysterectomy performed by her ObGyn. Surgery went well but the patient continued to report symptoms. A year later, she underwent an oophorectomy. Two years later, the patient reported blood in her urine and underwent a computed tomography scan, which revealed an obstructed left ureter that had caused injury to the left kidney. Seven months later, the kidney was removed.

PATIENT'S CLAIM: Her kidney loss was a direct result of the ObGyn's initial surgical procedure. He had placed several clips near the ureter and did not verify their position or protect the ureter. He also failed to address her reported symptoms in a timely manner.

PHYSICIAN'S DEFENSE: The damage to the ureter is a known risk of hysterectomy and oophorectomy. The obstruction developed over time, not as an immediate result of the surgery.

VERDICT: A Kentucky defense verdict was returned.

History of shoulder dystocia, Erb's palsy: $1.2M settlement

An obese mother was admitted to the hospital at 39 weeks' gestation with signs of labor. She requested a CD and was advised that she had progressed too far for that to be an option, and that vaginal delivery would be safe. During the second stage of labor, shoulder dystocia was encountered. The ObGyn made several attempts to deliver using downward traction, but was unsuccessful. A second ObGyn swept the shoulder with an internal maneuver of his hand and delivered the baby. The child has a severe brachial plexus injury at multiple spinal levels resulting in Erb's palsy.

PARENT'S CLAIM: A CD should have been performed. The first ObGyn failed to provide a CD and repeatedly applied excessive downward traction, causing the infant's injury.

PHYSICIAN'S DEFENSE: Shoulder dystocia is unpredictable and an unpreventable obstetric emergency. The ObGyn used proper maneuvers to release the shoulder dystocia.

VERDICT: A $1.2 million Virginia settlement was reached.

Ureter injured during hysterectomy

When a patient was found to have multiple, symptomatic fibroids and an enlarged uterus, her gynecologist suggested a total laparoscopic hysterectomy. During the procedure, when he inspected the pelvis and found multiple fibroids in and around the uterus, the gynecologist converted to a supracervical hysterectomy. Surgery was difficult because of a large myoma on the right broad ligament.

The patient tolerated surgery well and was released home the next day. At follow-up one week later, she had no signs or symptoms of ureter injury. Later that same evening, she experienced sharp flank pain and nausea. When she called the gynecologist, he sent her to the emergency department. A computed tomography scan showed extravasation of the right ureter. She underwent months of stent placements and replacements, nephrostomies, and ultimately ureteral reimplantation surgery.

PATIENT'S CLAIM: The gynecologist caused a thermal injury to her right ureter during the hysterectomy by misusing an electrocautery device. There was a delay in timely diagnosis postsurgery.

PHYSICIAN'S DEFENSE: The gynecologist contended that he employed proper surgical technique, and that he reacted properly when the patient reported the pain.

VERDICT: A Virginia defense verdict was returned. ●

LIVE CME/CE FROM

Global Academy for Medical Education

DIGESTIVE DISEASES

6TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

March 15-16, 2019
The Westin Philadelphia
Philadelphia, Pennsylvania

ABIM CME MOC ACCREDITED

Approved for
13.25 *AMA PRA Category 1 Credits™*
13.25 Pharmacy Contact Hours | 13.25 Nursing Contact Hours
AAFP Prescribed Credits

GlobalAcademyCME.com/Gastroenterology

MENTAL HEALTH

Current PSYCHIATRY | AACP AMERICAN ACADEMY OF CLINICAL PSYCHIATRISTS

PRESENT

PSYCHIATRY UPDATE 2019

SOLVING CLINICAL CHALLENGES, IMPROVING PATIENT CARE

MARCH 21-23, 2019
Pre-conference Addiction Workshop March 20
Chicago Marriott Downtown Magnificent Mile

21 CME/CE Credits Available

CPAACP-cme.com

SKIN DISEASE EDUCATION FOUNDATION PRESENTS

Save Up To $200 Until March 31!

15th Annual WOMEN'S & PEDIATRIC DERMATOLOGY SEMINAR®

JUNE 21-22, 2019
Fashion Island Hotel
Newport Beach
California

12.75 CME/CE + MOC-D Credits Available

GlobalAcademyCME.com/WPD

PRIMARY CARE/EMERGENCY CARE

Created especially for primary care physicians, NPs, and PAs

Created Especially for PAs, NPs & Primary Care Physicians!

ORIGINAL EMERGENCY MEDICINE BOOT CAMP

THE CORE EM KNOWLEDGE BASE

JULY 10-13, 2019
Caesars Palace
Las Vegas, Nevada

26 CME Credits Available

EMBootcamp.com/cme

To register and for complete information, including accreditation information, please see our websites.

PRODUCT Update

TREATMENT FOR VASOMOTOR SYMPTOMS

BIJUVA™ has been US Food and Drug Administration (FDA)–approved as the first oral treatment for moderate-to-severe vasomotor symptoms due to menopause in women with a uterus. **BIJUVA** offers a combination of bioidentical estradiol to reduce moderate-to-severe hot flashes and bioidentical progesterone to reduce the risk for endometrial hyperplasia.

TherapeuticsMD says that **BIJUVA** will be available Spring 2019 and is a proven treatment option for women who are experiencing bothersome symptoms of menopause, with clinical trial data demonstrating a statistically significant reduction in both the frequency and severity of moderate-to-severe vasomotor symptoms. The manufacturer also says that **BIJUVA** is developed to be identical in molecular structure to the hormones already produced by the body and is designed to help women restore what is lost during menopause.

BIJUVA estradiol and progesterone combination (1 mg/100 mg) will be available in capsule form.

FOR MORE INFORMATION, VISIT:
https://bijuva.com/discover/

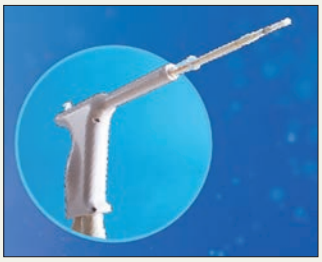
LILETTA USE EXTENDED

The FDA has approved **LILETTA**® (levonorgestrel-releasing intrauterine system) 52 mg for 5-year use. This approval is based on efficacy and safety data from **ACCESS US**, the largest ongoing intrauterine device (IUD) Phase 3 clinical trial in the United States. Previously, **LILETTA** was indicated for use up to 4 years.

LILETTA continues to be greater than 99% effective in preventing pregnancy in a broad range of women, regardless of age, race, body mass index, or parity, according to **Allergan and Medicines360.** The extended duration and proven efficacy across a diverse population enables more women in the United States to obtain effective birth control, as the IUD is now available for a low cost at public health clinics.

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

ENDOMETRIAL ABLATION TECHNOLOGY



AEGEA Medical introduces the **AEGEA Vapor System**™, an innovative solution for endometrial ablation to treat menorrhagia.

The system uses Adaptive Vapor Ablation and is the first endometrial ablation system specifically designed for use in the doctor's office, allowing minimal anesthesia/analgesia and rapid recovery, says **AEGEA Medical**. This is the first endometrial ablation technology to address the issue of postprocedure uterine cavity access.

AEGEA Medical describes the **AEGEA Vapor System** as a fully automated safety monitoring and vapor delivery system that uses a slender, flexible Vapor Probe with **SmartSeal**™ technology and the **Integrity Pro**™ safety feature, for an added level of confidence. The 4-minute procedure time includes 2 minutes of vapor treatment and can be performed in patients with a wider range of uterine anatomies than indicated for use with currently available treatments, says **AEGEA Medical**.

FOR MORE INFORMATION, VISIT: http://aegeamedical.com/

NATURAL CYCLES

The FDA has cleared **Natural Cycles** as the first digital method of birth control in the United States. Delivered in the form of an app, **Natural Cycles** is a fertility awareness–based contraceptive that uses a sophisticated algorithm to accurately and conveniently determine a woman's daily fertility based on basal body temperature.

That data builds into a personalized fertility indicator that informs her when she needs to use protection to minimize the chance of conception. The app also can be used to help plan a pregnancy when the time is right, according to **Natural Cycles**.

A clinical study showed that the efficacy of a contraceptive mobile application is higher than usually reported for traditional fertility awareness–based methods. The application may contribute to reducing the unmet need for contraception, says **Natural Cycles**.

FOR MORE INFORMATION, VISIT:
https://www.naturalcycles.com/en/hcp

Tell us what you think!

Share your thoughts on an article or on any topic relevant to ObGyns and women's health practitioners.

We will consider publishing your letter in a future issue.

Send your letter to:
rbarbieri@mdedge.com

Please include the city and state in which you practice.

Stay in touch! Your feedback is important to us!

A patient with severe adenomyosis requests uterine-sparing surgery

CONTINUED FROM PAGE 37

2004;57:132-138.
35. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedures. *Fertil Steril*. 1991;55:700-704.
36. Luciano AA, Maier DB, Koch EI, et al. A comparative study of postoperative adhesions following laser surgery by laparoscopy versus laparotomy in the rabbit model. *Obstet Gynecol*. 1989;74:220-224.
37. Lundorff P, Hahlin M, Källfelt B, et al. Adhesion formation after laparoscopic surgery in tubal pregnancy: a randomized trial versus laparotomy. *Fertil Steril*. 1991;55:911-915.
38. Kwack JY, Kwon YS. Laparoscopic surgery for focal adenomyosis. *JSLS*. 2017;21. pii:e2017.00014.
39. Podratz K. *Degrees of Freedom: Advances in Gynecological and Obstetrical Surgery. Remembering Milestones and Achievements in Surgery: Inspiring Quality for a Hundred Years 1913–2012*. Chicago, IL: American College of Surgeons; 2012.
40. Nezhat C, Nezhat F, Bess O, et al. Laparoscopically assisted myomectomy: a report of a new technique in 57 cases. *Int J Fertil Menopausal Stud*. 1994;39:39-44.

INDEX OF ADVERTISERS

*Demographic advertisement.

CONTINUED FROM PAGE 52

health outcomes. Investigators used medical records to confirm health outcomes.

After adjusting for covariates, no significant differences in risks were found for CVD, cancer, and hip fracture between users and nonusers of vaginal estrogen, regardless of hysterectomy status.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Despite the boxed warning on vaginal estrogen, the findings from this study support the safety of vaginal estrogen use for effective relief of GSM in women with and without a uterus.

JOANN V. PINKERTON, MD, NCMP

Key findings

After adjusting for multiple variables (including age, race, physical activity, age at menopause, hysterectomy, aspirin use, parental history of cancer, etc), health outcomes for CVDs, all cancers, and hip fracture were:

- myocardial infarction: hazard ratio (HR), 0.73 (95% confidence interval [CI], 0.47–1.13)
- stroke: HR, 0.85 (95% CI, 0.56–1.29)
- pulmonary embolism/deep vein thrombosis: HR, 1.06 (95% CI, 0.58–1.93)
- hip fracture: HR, 0.91 (95% CI, 0.60–1.38)
- all cancers: HR, 1.05 (95% CI, 0.89–1.25).

Health outcomes for specific invasive cancers (risk for endometrial cancer included only women with an intact uterus) were:

- invasive breast cancer: HR, 1.07 (95% CI, 0.78–1.47)
- ovarian cancer: HR, 1.17 (95% CI, 0.52–2.65)
- endometrial cancer: HR, 1.62 (95% CI, 0.88–2.97)
- colorectal cancer: HR, 0.77 (95% CI, 0.45–1.34).

Study strengths and weaknesses

A causal relationship cannot be proven as the study was observational. However, a strength included the 18 years of follow-up. Women used vaginal estrogen for an average of 3 years, which provided longer-term safety data than available 12-month clinical trial data. Data were collected through self-report on questionnaires every 2 years, which is a drawback; however, participants were registered nurses, who have been shown to provide reliable health-related information. Comparisons between therapies were not possible as data were not collected about type or dosage of vaginal estrogen. Available therapies during the NHS included vaginal estrogen tablets, creams, and an estradiol ring, with higher doses available during earlier parts of the study than the lower doses commonly prescribed in current day.

Overall

The findings from this long-term follow-up of the NHS provide support for the safety of vaginal estrogen for treatment of GSM. No statistically significant increased health risks were found for users of vaginal estrogen, similar to earlier reported findings from the large Women's Health Initiative.[2] Low-dose vaginal estrogen is recommended for treatment of GSM by The North American Menopause Society, the American College of Obstetricians and Gynecologists, and the Endocrine Society.

Absorption of low-dose vaginal estrogen preparations appears minimal, and they are effective and generally safe for the treatment of GSM for women at any age. Progesterone is not recommended with low-dose vaginal estrogen therapies, based primarily on randomized clinical trial safety data of 12 months.[3] Postmenopausal bleeding, however, needs to be thoroughly evaluated. For women with breast cancer, include the oncologist in decision making about the use of low-dose vaginal estrogen. ●

FAST TRACK

Low-dose vaginal estrogen is effective and generally safe for treating GSM in women of any age

References

1. Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol.* 2016;251:704-711.
2. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause.* 2018;25:11-20.
3. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24:728-753.

Is vaginal estrogen used for GSM associated with a higher risk of CVD or cancer?

No. Vaginal estrogen use (average duration of use, 37.5 months) for genitourinary symptoms of menopause (GSM) was not associated with a higher risk of cardiovascular disease (CVD) or cancer in nonusers of systemic hormone therapy in the Nurses' Health Study. During 18 years of follow-up for the almost 900 postmenopausal users of vaginal estrogen, compared with about 53,000 nonusers, the risks of CVD, cancers, and hip fractures were not different between groups. Presence or absence of a uterus did not change the study results.

FAST TRACK

The package label for low-dose vaginal estrogen warns of chronic disease risks with use despite lack of observational data or trial evidence to support the warning

EXPERT COMMENTARY
JoAnn V. Pinkerton, MD, NCMP is Professor of Obstetrics and Gynecology, University of Virginia Health System, and Executive Director, The North American Menopause Society. Dr. Pinkerton serves on the OBG MANAGEMENT Board of Editors.

Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. Menopause. December 17, 2018. doi: 10.1097/GME.0000000000001284.

GSM, a chronic and often progressive condition, occurs in almost 50% of postmenopausal women and has been shown to impair sexual function and quality of life.[1] Symptoms include vaginal dryness, vulvar or vaginal itching, dyspareunia, urinary urgency or frequency, and increased urinary tract infections. Although lubricants or vaginal moisturizers may be sufficient to treat GSM, targeted hormonal therapy may be needed to improve the symptoms and resolve the underlying cause, due to vaginal hormone loss.

The author reports no financial relationships relevant to this article.

Despite lack of any observational or clinical trial evidence for chronic health disease risks related to low-dose vaginal estrogen use, there remains an US Food and Drug Administration boxed warning on the package label for low-dose vaginal estrogen related to risks of heart disease, stroke, venous thromboembolism, pdementia, and breast cancer. The objective of the investigation by Bhupathiraju and colleagues was to evaluate associations between vaginal estrogen use and health outcomes, including CVD (myocardial infarction, stroke, and pulmonary embolism/deep vein thrombosis), cancer (total invasive, breast, endometrial, ovarian, and colorectal), and hip fracture.

Details of the study

The prospective analysis included 896 postmenopausal current users of vaginal estrogen in the Nurses' Health Study (NHS; 1982–2012), compared with 52,901 nonusers. Eighteen years of follow-up was evaluated. Users of systemic hormone therapy were excluded from the analysis. For the NHS, self-reported data were collected every 2 years on questionnaires for vaginal estrogen use and

CONTINUED ON PAGE 51

Have you visited **mdedge.com/obgyn** this week?

Is salpingectomy (vs standard tubal ligation) for sterilization a feasible option at cesarean delivery?
John T. Repke, MD

Patient-centric pain management decision aid reduces opioid use posthysterectomy
Kathy Christie, Senior Editor

Nationwide implementation of MIS reduced complications and increased survival in early-stage endometrial cancer
Lila O'Connor, Editor

The art of manipulation: Simplifying hysterectomy by preparing the learner
Isabel C. Green, MD; Michelle Wyatt, MD; and Tatnai Burnett, MD
Brought to you by the Society of Gynecologic Surgeons

Addressing your patient's sexual function after cancer
Stacy Tessler Lindau, MD

New and promising GSM treatments, more clinical takeaways from NAMS 2018
Gloria A. Richard-Davis, MD, MBA

Vaginal and bilateral thigh removal of a transobturator sling
Elise Bardawil, MD; Joie Guner, MD, MSc; Evelyn Pan, BS; and Francisco Orejuela, MD
Brought to you by the Society of Gynecologic Surgeons

Maternal immunization: What does the future hold?
Kevin Ault, MD

The opioid crisis: Treating pregnant women with addiction
Mishka Terplan, MD, MPH

How is gene study adding to the overall knowledge of preterm birth?
Q&A with Louis J. Muglia, MD, PhD

Plus, visit us online for daily news!

OBG MANAGEMENT

Of course, current and past articles are still there for you—in full text and as convenient, downloadable PDF files. And you'll find an easy way to contact us.

HOLOGIC®

Don't wonder

if sending her home is the right decision...

Be confident

that it is.

With a

99.5% NPV,

fFN testing can help you identify which patients with symptoms of preterm labor you can confidently send home.[1]

RapidfFN®

Reference: 1. Rapid fFN for the TIi_{Q} System [package insert]. AW-04196-001, Rev. 004, Sunnyvale, CA: Hologic, Inc.; 2017