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OBG MANAGEMENT

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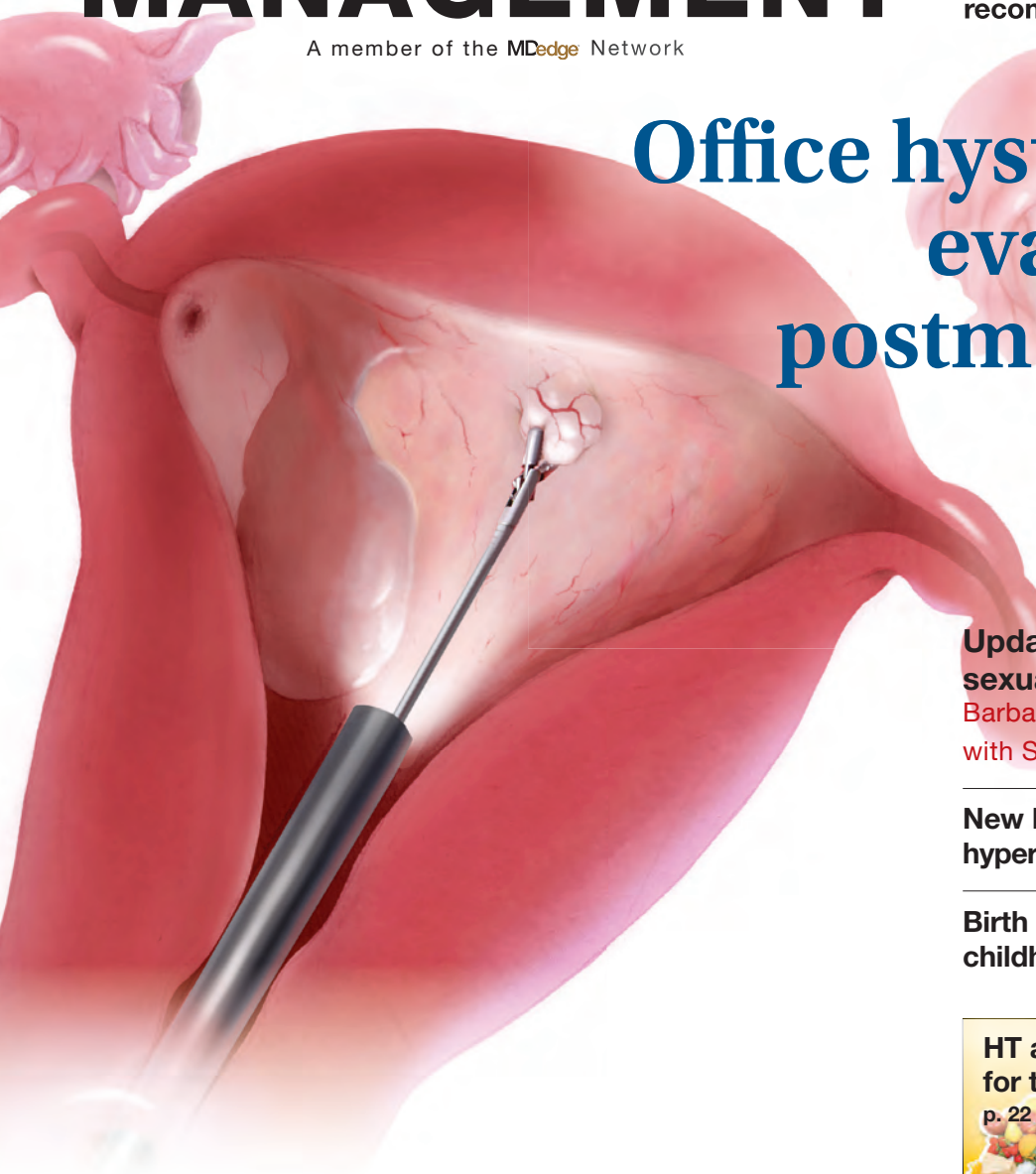

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Update on female sexual dysfunction
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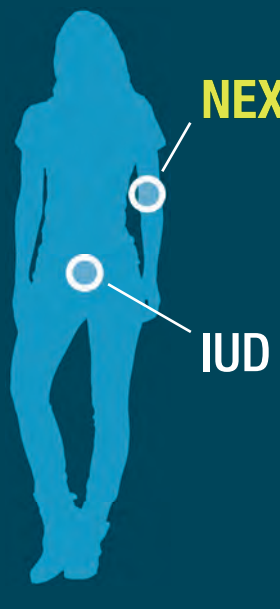

Help your patients understand both of their LARC location options[1]

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

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

US-XPL-00588 05/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

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

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

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

Nexplanon®
(etonogestrel implant) 68mg

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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-1810r020
Revised: 10/2018

MERCK

#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 June 2019, Obstetrics/Gynecology Combined Office & Hospital Readers.

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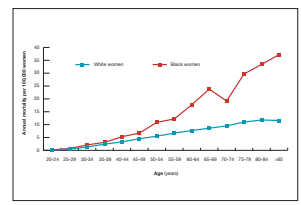

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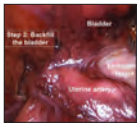

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CHRISTINE FOLEY, MD, AND NICOLE DONNELLAN, MD

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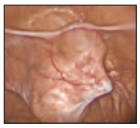

Novel method to demarcate bladder dissection during posthysterectomy sacrocolpopexy

KATHRYN L. DENGLER, MD; CHRISTOPHER STRAUCHON, DO; HECTOR M. GONZALEZ, MD; AND DANIEL D. GRUBER, MS, MD

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Why do so many women aged 65 years and older die of cervical cancer?

Many women aged >65 years who are at risk for cervical cancer are not being actively screened, resulting in a high rate of cervical cancer mortality after 65 years of age

Robert L. Barbieri, MD
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Surprisingly, the cervical cancer death rate is greater among women aged >65 years than among younger women[1,2] (**FIGURE**, page 8). Paradoxically, most of our screening programs focus on women <65 years of age. A nationwide study from Denmark estimated that the cervical cancer death rate per 100,000 women at ages 40 to 44 and 65 to 69 was 3.8 and 9.0, respectively.[1] In other words, the cervical cancer death rate at age 65 to 69 years was 2.36 times higher than at age 40 to 44 years.[1]

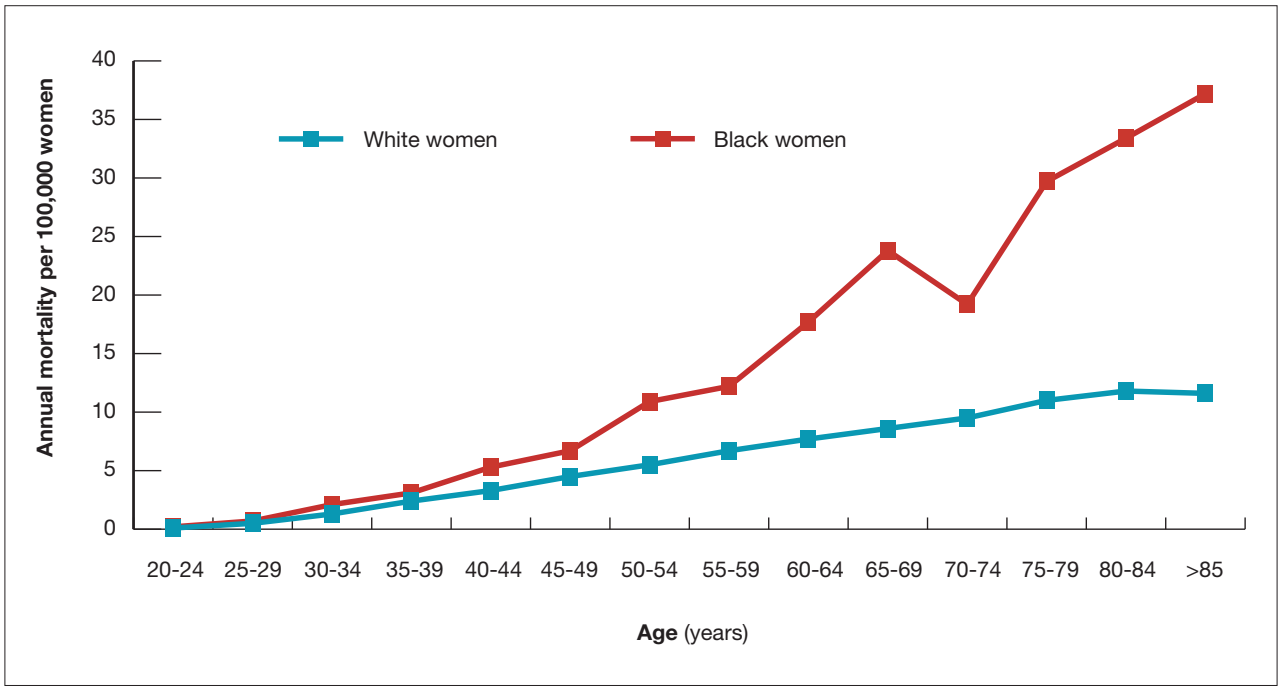
A study from the United States estimated that the cervical cancer death rate per 100,000 white women at ages 40 to 44 and 65 to 69 was 3.3 and 8.6, respectively,[2] very similar to the findings from Denmark. The same US study estimated that the cervical cancer death rate per 100,000 black women at ages 40 to 44 and 65 to 69 was 5.3 and 23.8, highlighting the fact that, in the United States, cervical cancer disease burden is disproportionately greater among black than among white women.[2] In addition, the cervical cancer death rate among black women at age 65 to 69 was 4.49 times higher than at age 40 to 44 years.[2]

Given the high death rate from cervical cancer in women >65 years of age, it is paradoxical that most professional society guidelines recommend discontinuing cervical cancer screening at 65 years of age, if previous cervical cancer screening is normal.[3,4] Is the problem due to an inability to implement the current guidelines? Or is the problem that the guidelines are not optimally designed to reduce cervical cancer risk in women >65 years of age?

The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPSTF) recommend against cervical cancer screening in women >65 years of age who have had adequate prior screening and are not otherwise at high risk for cervical cancer. However, ACOG and the USPSTF caution that there are many groups of women that may benefit from continued screening after 65 years of age, including women with HIV infection, a compromised immune system, or previous high-grade precancerous lesion or cervical cancer; women with limited access to care; women from racial/ethnic minority groups; and migrant women.[4] Many clinicians remember the guidance, "discontinue cervical cancer screening at 65 years" but do not recall all the clinical factors that might warrant continued screening past age 65. Of special concern is that black,[2] Hispanic,[5] and migrant women[6] are at much higher risk for invasive cervical cancer than white or US-born women.

The optimal implementation of the ACOG and USPSTF guidelines are undermined by a fractured health care system, where key pieces of information may be unavailable to the clinician tasked with making a decision about discontinuing cervical cancer screening. Imagine the case in which a 65-year-old woman presents to her primary care physician for cervical cancer screening. The clinician performs a cervical cytology test and obtains a report of "no intraepithelial lesion or malignancy." The clinician then recommends that the patient discontinue cervical cancer screening. Unbeknownst to the clinician, the patient had a positive

FIGURE Age-specific, hysterectomy-corrected cervical cancer mortality rates in white and black US women[2]



HPV 16/18/45 test within the past 10 years in another health system. In this case, it would be inappropriate to terminate the patient from cervical cancer screening.

Testing for hrHPV is superior to cervical cytology in women >65 years

In Sweden, about 30% of cervical cancer cases occur in women aged >60 years.[7] To assess the prevalence of oncogenic high-risk HPV (hrHPV), women at ages 60, 65, 70, and 75 years were invited to send sequential self-collected vaginal samples for nucleic acid testing for hrHPV. The prevalence of hrHPV was found to be 4.4%. Women with a second positive, self-collected, hrHPV test were invited for colposcopy, cervical biopsy, and cytology testing. Among the women with two positive hrHPV tests, cervical biopsy revealed 7 cases of cervical intraepithelial neoplasia grade 2 (CIN2), 6 cases of CIN1, and 4 biopsies without CIN. In these women 94% of the cervical cytology samples returned, "no intraepithelial lesion or malignancy" and 6% revealed atypical squamous cells of undetermined significance. This study suggests that, in women aged >65 years, cervical cytology may have a high rate of false-negative results, possibly due to epithelial atrophy. **An evolving clinical pearl is that, when using the current cervical cancer screening guidelines, the final screen for cervical cancer must include a nucleic acid test for hrHPV.**

In women 65 to 90 years, the prevalence of hrHPV is approximately 5%

In a study of 40,382 women aged 14 to 95 years, the prevalence of hrHPV was 46% in 20- to 23-year-old women and 5.7% in women older than 65 years of age.[8] In a study of more than 108,000 women aged 69 to >89 years the prevalence of hrHPV was 4.3%, and similar prevalence rates were seen across all ages from 69 to >89 years.[9] The carcinogenic role of persistent hrHPV infection in women >65 years is an important area for future research.

Latent HPV virus infection

Following a primary varicella-zoster infection (chickenpox), the virus may remain in a latent state in sensory ganglia, reactivating later in life to cause shingles. Thirty percent of people who have a primary chickenpox infection eventually will develop a case of shingles. Immunocompromised populations are at an increased risk of developing shingles because of reduced T-cell mediated immunity.

A recent hypothesis is that in immunocompromised and older

women, latent HPV can reactivate and cause clinically significant infection.[10] Following renal transplantation investigators have reported a significant increase in the prevalence of genital HPV, without a change in sexual behavior.[11] In cervical tissue from women with no evidence of active HPV infection, highly sensitive PCR-based assays detected HPV16 virus in a latent state in some women, possibly due to disruption of the viral E2 gene.[12] If latent HPV infection is a valid biological concept, it suggests that there is no "safe age" at which to discontinue screening for HPV infection because the virus cannot be detected in screening samples while it is latent.

Options for cervical cancer screening in women >65 years

Three options might reduce the morbidity and mortality associated with cervical cancer in women >65 years.

Option 1: Double-down on trying to effectively implement current guidelines. The high rate of cervical cancer mortality in women >65 years of age indicates that the current guidelines, as implemented in real clinical practice, are not working. A problem with the current screening guidelines is that clinicians are expected to be capable of finding all relevant cervical cancer test results and properly interpreting the results. Clinicians are over-taxed and fallible, and the current approach is not likely to be successful unless additional information technology solutions are implemented.

Health systems could use information technology to mitigate these problems. For example, health systems could deploy software to assemble every cervical screening result on each woman and present those results to clinicians in a single integrated view in the electronic record. Additionally, once all lifetime screening results are consolidated in one view, artificial intelligence systems could be used to analyze the totality of results and identify women who would benefit by continued screening past age 65 and women who could safely discontinue screening.

Option 2: Adopt the Australian approach to cervical cancer screening. The current Australian approach to cervical cancer screening is built on 3 pillars: 1) school-based vaccination of all children against hrHPV, 2) screening all women from 25 to 74 years of age every 5 years using nucleic acid testing for hrHPV, and 3) providing a system for the testing of samples self-collected by women who are reluctant to visit a clinician for screening.[13] Australia has one of the lowest cervical cancer death rates in the world.

Option 3: Continue screening most women past age 65. Women >65 years of age are known to be infected with hrHPV genotypes. hrHPV infection causes cervical cancer. Cervical cancer causes many

Vaccination to prevent cancer is superior to screening and treating cancer

In 2008, Harald zur Hausen, MD, received the Nobel Prize in Physiology or Medicine for discovering that human papilloma virus (HPV) caused cervical cancer. In a recent study, 74% of cervical cancers were associated with HPV 16 or 18 infections. A total of 89% of the cancers were associated with one of the high-risk HPV genotypes, including HPV 16/18/31/33/45/52/58.[1]

Recently, HPV has been shown to be a major cause of oropharyngeal cancer. The Centers for Disease Control and Prevention calculated that in CY2015 in the United States there were 18,917 cases of HPV-associated oropharyngeal squamous cell cancer and 11,788 cases of cervical cancer.[2] Most cases of HPV-associated oropharyngeal cancer occur in men, and HPV vaccination of boys may help to prevent this cancer type. Oncogenic HPV produce two proteins (E6 and E7) that promote viral replication and squamous cell growth by inhibiting the function of p53 and retinoblastoma protein. The immortalized HeLa cell line, derived from Ms. Henrietta Lack's cervical cancer, contains integrated HPV18 nucleic acid sequences.[3,4]

The discovery that HPV causes cancer catalyzed the development of nucleic acid tests to identify high-risk oncogenic HPV and vaccines against high-risk oncogenic HPV genotypes that prevent cervical cancer. From a public health perspective, it is more effective to vaccinate the population against oncogenic HPV genotypes than to screen and treat cancer. In the United States, vaccination rates range from a high of 92% (District of Columbia) and 89% (Rhode Island) to a low of 47% (Wyoming) and 50% (Kentucky and Mississippi).[5] To reduce HPV-associated cancer mortality, the gap in vaccination compliance must be closed.

References

1. Kjaer SK, Munk C, Junge J, et al. Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ACSUC/LSIL, HSIL, or cervical cancer: what is the potential for prevention? *Cancer Causes Control.* 2014;25:179-189.
2. Van Dyne EA, Henley SJ, Saraiya M, et al. Trends in human papillomavirus-associated cancers - United States, 1999-2015. *MMWR Morb Mortal Wkly Rep*. 2018;67:918-924.
3. Rosl F, Westphal EM, zur Hausen H. Chromatin structure and transcriptional regulation of human papillomavirus type 18 DNA in HeLa cells. *Mol Carcinog.* 1989;2:72-80.
4. Adey A, Burton JN, Kitzman, et al. The haplotype-resolved genome and epigenome of the aneuploid HeLa cancer cell line. *Nature.* 2013;500:207-211.
5. Walker TY, Elam-Evans LD, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years - United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2017;66:874-882.

deaths in women aged >65 years. There is no strong rationale for ignoring these three facts. hrHPV screening every 5 years as long as the woman is healthy and has a reasonable life expectancy is an option that could be evaluated in randomized studies.

Given the high rate of cervical cancer death in women >65 years of age, I plan to be very cautious about discontinuing cervical cancer screening until I can personally ensure that my patient has no evidence of hrHPV infection. ●

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

References

1. Hammer A, Kahlert J, Gravitt PE, et al. Hysterectomy-corrected cervical cancer mortality rates in Denmark during 2002-2015: a registry-based cohort study. *Acta Obstet Gynecol Scand*. 2019;98:1063-1069.
2. Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. *Cancer*. 2017;123:1044-1050.
3. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 168: cervical cancer screening and prevention. *Obstet Gynecol*. 2016;128:e111-30.
4. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320:674-686.
5. Stang A, Hawk H, Knowlton R, et al. Hysterectomy-corrected incidence rates of cervical and uterine cancers in Massachusetts, 1995-2010. *Ann Epidemiol*. 2014;24:849-854.
6. Hallowell BD, Endeshaw M, McKenna MT, et al. Cervical cancer death rates among U.S.- and foreign-born women: U.S., 2005-2014. *Am J Prev Med*. 2019;56:869-874.
7. Lindström AK, Hermansson RS, Gustavsson I, et al. Cervical dysplasia in elderly women performing repeated self-sampling for HPV testing. *PLoS One*. 2018;13:e0207714.
8. Kjaer SK, Munk C, Junge J, et al. Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ACSUC/LSIL, HSIL, or cervical cancer: what is the potential for prevention? *Cancer Causes Control*. 2014;25:179-189.
9. Andersen B, Christensen BS, Christensen J, et al. HPV-prevalence in elderly women in Denmark. *Gynecol Oncol*. 2019;154:118-123.
10. Gravitt PE, Winer RL. Natural history of HPV infection across the lifespan: role of viral latency. *Viruses*. 2017;9:E267.
11. Hinten F, Hilbrands LB, Meeuwis KAP, et al. Reactivation of latent HPV infections after renal transplantation. *Am J Transplant*. 2017;17:1563-1573.
12. Leonard SM, Pereira M, Roberts S, et al. Evidence of disrupted high-risk human papillomavirus DNA in morphologically normal cervices of older women. *Sci Rep*. 2016;6:20847.
13. Cervical cancer screening. Cancer Council website. https://www.cancer.org.au/about-cancer/early-detection/screening-programs/cervical-cancer-screening.html. Updated March 15, 2019. Accessed July 23, 2019.

How do new BP guidelines affect identifying risk for hypertensive disorders of pregnancy?

An analysis of blood pressure (BP) data from 8,899 nulliparous women, based on recently redefined lower threshold categories of normal (< 120/80 mm Hg), elevated (120–129 mm Hg systolic and < 80 mm Hg diastolic), and stage 1 hypertension (130–139 mm Hg systolic or 80–89 mm Hg diastolic), found that **increasing BP category was associated with a higher risk of all hypertensive disorders of pregnancy**. In addition, an **upward BP trajectory** (≥ 5 mm Hg), compared with a downward trajectory (≤ -5 mm Hg), **was significantly associated with risk of hypertensive disorders of pregnancy** (*P*<.001).

FAST TRACK

In the 1993 NIH preeclampsia prevention trial, initial systolic BP of 120 to 134 mm Hg and initial weight of >60 kg were the factors most associated with developing preeclampsia

Hauspurg A, Parry S, Mercer BM, et al. Blood pressure trajectory and category and risk of hypertensive disorders of pregnancy in nulliparous women. Am J Obstet Gynecol. 2019. pii: S0002-9378(19)30807-5. doi: 10.1016/j.ajog.2019.06.031.

EXPERT COMMENTARY

John T. Repke, MD, is Professor Emeritus, Obstetrics and Gynecology, Penn State University College of Medicine, Hershey, Pennsylvania. He serves on the OBG MANAGEMENT Board of Editors.

Hauspurg and colleagues set out to determine whether redefined BP category (normal, < 120/80 mm Hg) and trajectory (a difference of ≥ 5 mm Hg systolic, diastolic, or mean arterial pressure between the first and second prenatal visit) helps to identify women at increased risk for developing hypertensive disorders of pregnancy or preeclampsia.

With respect to the former variable, such an association was demonstrated in the first National Institutes of Health–funded preeclampsia prevention trial published in 1993, which used low-dose aspirin.[1] In that trial, low-dose aspirin was not found to be effective in preventing preeclampsia in young, healthy nulliparous women. Interestingly, the 2 factors most associated with developing preeclampsia were an initial systolic BP of 120 to 134 mm Hg and an initial weight of >60 kg. For most clinicians, these findings would not be helpful in trying to better identify a high-risk group.

The author reports no financial relationships relevant to this article.

Details of the study

The idea of BP "trajectory" is interesting in the Hauspurg and colleagues' study. The authors analyzed data from the Nulliparous

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Until further data are available, my advice to clinicians is to pay close attention to all risk factors for any of the hypertensive disorders of pregnancy. Initial BP and BP trajectory are important but probably something that sound clinical judgment would identify anyway. My recommendation is to continue to use those methods of prophylaxis, fetal surveillance, and indications for delivery that are supported by current data and await the additional investigations that Hauspurg and colleagues suggest need to be done before altering your management of women at increased risk for any of the hypertensive disorders of pregnancy.

JOHN T. REPKE, MD

FAST TRACK

Elevated BP was associated with an aRR of 1.54 (95% CI, 1.18–2.02) and stage 1 hypertension was associated with an aRR of 2.16 (95% CI, 1.31–3.57) for any hypertensive disorder of pregnancy

Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), a prospective cohort study, and included a very large population of almost 9,000 women in the analysis. Participants were classified according to their BP measurement at the first study visit, with BP categories based on updated American College of Cardiology/American Heart Association guidelines. The primary outcome was the risk of hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia.

The data analysis found that elevated BP was associated with an adjusted risk ratio (aRR) of 1.54 (95% confidence interval [CI], 1.18–2.02). Stage 1 hypertension was associated with an aRR of 2.16 (95% CI, 1.31–3.57). Compared with women whose BP had a downward systolic trajectory, women with normal BP and an upward systolic trajectory had a 41% increased risk of any hypertensive disorder of pregnancy (aRR, 1.41; 95% CI, 1.20–1.65).

Study strengths and limitations

While the large study population is a strength of this study, there are a number of limitations, such as the use of BP measurements during pregnancy only, without having prepregnancy measurements available. Further, a single BP measurement during each visit is also a drawback, although the standardized measurement by study staff is a strength.

Anticlimactic conclusions. The conclusions of the study, however, are either not surprising, not clinically meaningful, or of little value to clinicians at present, at least with respect to patient management.

Conclusions that were not surprising included a statistically lower chance of indicated preterm delivery in the normal BP group than in the elevated BP or stage 1 hypertension groups. Conclusions that were not meaningful included a statistically significant lower birthweight in the elevated BP group (3,269 g) and in the stage 1 hypertension group (3,258 g) compared with the normal BP group (3,279 g), but the clinical significance of these differences is arguable.

Lastly is the issue of what these data mean for clinical practice. The idea of identifying high-risk groups is attractive, provided that there are effective intervention strategies available. If one follows the United States Preventive Services Task Force (USPSTF) recommendations for preeclampsia prevention,[2] then virtually every nulliparous woman is a candidate for low-dose aspirin for preeclampsia prophylaxis. Beyond that, the current data do not support any change in the standard clinical practice of managing these "now identified" high-risk women. Increasing prenatal visits, using biomarkers to further delineate risk, and using uterine artery Doppler studies are all strategies that have been or are being investigated, but as yet they are not supported by conclusive data documenting improved outcomes—a sentiment supported by both the USPSTF[3] and the authors of the study. ●

References

1. Sibai BM, Caritis SN, Thom E, et al; National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine. Prevention of preeclampsia with low-dose aspirin in healthy nulliparous pregnant women. *N Engl J Med*. 1993;329:1213-1218.
2. United States Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: preventive medication. September 2014. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-preeclampsia-preventive-medication. Accessed July 30, 2019.
3. United States Preventive Service Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for preeclampsia: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;387:1661-1667.

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PRE-CONFERENCE WORKSHOPS
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WORKSHOP A 8:30 AM – 12:30 PM
Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques NEW!
Led by: Rosanne M. Kho, MD
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WORKSHOP B 8:30 AM – 12:30 PM
Hands-On Laparoscopic Suturing - The "Vertical Zone" (Simulation Lab)
Led by: Charles H. Koh, MD
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WORKSHOP C 8:30 AM – 5:30 PM
Office-Based Gynecologic Procedures
All day workshop (Includes a morning lecture series and afternoon practicum.)
Led by: Tommaso Falcone, MD
8 CME Credits Available

WORKSHOP D 1:30 PM – 5:30 PM
Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
Led by: Mickey M. Karram, MD
4 CME Credits Available

GENERAL SCIENTIFIC SESSIONS

THURSDAY, DECEMBER 12, 2019

6:45 AM **Registration/Breakfast/Exhibits**

7:50 AM **Course Overview**
Mickey M. Karram, MD

PELVIC ANATOMY

8:00 AM **Pelvic and Abdominal Anatomy from the Laparoscopic Surgeon's View**
Tommaso Falcone, MD

8:40 AM **Anatomic Considerations: Facilitating Vaginal Procedures Safely and Effectively**
Mickey M. Karram, MD

INCONTINENCE AND PROLAPSE SURGERY

9:10 AM **Panel Discussion: Evaluation and Non-Surgical Management of Female Pelvic Floor Disorders: What Every Generalist Should Know**
John B. Gebhart, MD, MS
Mickey M. Karram, MD
Beri M. Ridgeway, MD

9:55 AM **Question and Answer Session**

10:25 AM **Break/Exhibits**

11:25 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

12:05 PM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD, MS

12:25 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:55 PM **Question and Answer Session**

1:10 PM **Lunch**

1:25 PM **Luncheon Symposium**

2:10 PM **Dessert Break/ Exhibits**

THURSDAY'S KEYNOTE LECTURE

2:40 PM **The Evolution of Surgical Procedures Used to Correct Pelvic Organ Prolapse**
Mark D. Walters, MD

BENIGN GYNECOLOGY

3:25 PM **Safe Use of Energy-Based Devices for Gynecologic Surgery**
Andrew I. Brill, MD

3:55 PM **Management of Endometriosis**
Tommaso Falcone, MD

4:40 PM **The Hysteroscopic Treatment of Submucosal Fibroids and Polyps**
Linda D. Bradley, MD

5:10 PM **Question and Answer Session**

FRIDAY, DECEMBER 13, 2019

6:45 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

8:15 AM **The Difficult Vaginal Hysterectomy**
Rosanne M. Kho, MD

8:45 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:15 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

9:45 AM **Break /Exhibits**

10:30 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:00 AM **Tissue Extraction Techniques (Morcellation)**
Sawsan As-Sanie, MD, MPH

11:30 AM **Uterine Preserving Procedures in Patients with Pelvic Organ Prolapse**
Mickey M. Karram, MD
Beri M. Ridgeway, MD

12:00 PM **Enhanced Recovery after Surgery**
Sawsan As-Sanie, MD, MPH

12:30 PM **Question and Answer Session**

1:00 PM **Lunch**

1:15 PM **Luncheon Symposium**

2:00 PM **Dessert Break/Exhibits**

FRIDAY'S KEYNOTE LECTURE

2:30 PM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Mark D. Walters, MD

ONCOLOGY FOR THE GENERALIST

3:15 PM **Surgical Management of Pre-Cancer Vulvovaginal Lesions**
Amanda Nickles Fader, MD

4:00 PM **Laparoscopic and Robotic Management of the Adnexal Mass**
Javier F. Magrina, MD

4:45 PM **Spectrum of Vulvovaginal Disorders**
Michael S. Baggish, MD

5:30 PM **Question and Answer Session**

SATURDAY, DECEMBER 14, 2019

6:30 AM **Breakfast**

7:30 AM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

8:30 AM **Avoiding and Managing Urogynecologic Complications**
John B. Gebhart, MD, MS
Mickey M. Karram, MD

9:30 AM **Avoiding and Managing Laparoscopic Complications**
Tommaso Falcone, MD

10:30 AM **Break**

10:45 AM **Interesting Case Presentations in Medical Legal**
Michael S. Baggish, MD
Tommaso Falcone, MD

11:30 AM **Surgical Tips for Successful Pelvic Surgery: Video Session**
Surgical Management of Cornual Ectopic & Dermoid Cysts
Tommaso Falcone, MD

Techniques to Suspend the Apex at the Time of Vaginal Surgery
Mickey M. Karram, MD

1:00 PM **Question and Answer Session**

1:15 PM **PAGS Scientific Program Adjournment**

P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional)

Open to Non-Attendees So bring your staff!

3.25 CME Credits Available

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Director
Neil H. Baum, MD
Former Associate Clinical Professor of Urology
Tulane Medical School and Louisiana State University
New Orleans, Louisiana

Dr. Neil Baum is the author of *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

SATURDAY, DECEMBER 14, 2019 Encore at Wynn Las Vegas

2:00 PM **Course Overview**

2:10 PM
- The 4 Pillars of a Successful Practice
- How to Improve the Efficiency, Productivity, and Profitability of Your Practice
- Online Reputation Management
- Why Market and Promote Your ObGyn Practice

3:30 PM **Break**

3:45 PM
- Using Social Media to Get to the Top of Google
- Numbers You Need to Know
- Moving from Volume to Value

5:00 PM **Q and A**

5:30 PM **P.E.P. Adjournment**

PAGS Scientific Faculty

Course Chairs

Tommaso Falcone, MD
Chief of Staff
Chief Academic Officer
Medical Director
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
London, UK

Mickey M. Karram, MD
Director of Urogynecology
The Christ Hospital
Volunteer Professor of Ob/Gyn
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Mark D. Walters, MD
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Department of Obstetrics and Gynecology
Cleveland Clinic
Cleveland, Ohio

Faculty

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Phoenix, Arizona

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Department Chair, Regional Ob/Gyn
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Assistant Professor
Cleveland Clinic Learner College of Medicine
Cleveland, Ohio

Optional Workshops

For complete information please see PAGS-CME.org.

Wednesday, December 11, 2019, Encore at Wynn Las Vegas
Optional Hands-on Workshops
PAGS hands-on workshops have limited space available and will sell out. First come. First served!
(See PAGS website for complete workshop details.)

WORKSHOP A
ENERGY-BASED DEVICES FOR HYSTERECTOMY AND TISSUE EXTRACTION TECHNIQUES NEW!
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Rosanne M. Kho, MD
Faculty: Andrew I. Brill, MD; Keith B. Isaacson, MD

WORKSHOP B
HANDS-ON LAPAROSCOPIC SUTURING - THE "VERTICAL ZONE" (SIMULATION LAB)
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Charles H. Koh, MD

WORKSHOP C
OFFICE-BASED GYNECOLOGIC PROCEDURES: THE GYNECOLOGIST OF THE FUTURE
FULL-DAY WORKSHOP
8 CME Credits Available
8:30 AM - 5:30 PM
Includes a morning lecture series and afternoon practicum on vulvar/vaginal injections and excisions, ultrasound and hysteroscopy

Led by: Tommaso Falcone, MD
Faculty: Andrew Brill, MD; Linda D. Bradley, MD; Mark Dassel, MD; Jeffrey R. Dell, MD; Laura Detti, MD; Oluwatosin Goje, MD; Keith Isaacson, MD; Mickey Karram, MD; James M. Shwayder, MD, JD

WORKSHOP D
TECHNICAL ASPECTS OF VAGINAL HYSTERECTOMY & CYSTOURETHROSCOPY FOR THE GYNECOLOGIST
4 CME Credits Available
1:30 PM - 5:30 PM
Led by: Mickey M. Karram, MD
Faculty: Rosanne M. Kho, MD; Doug Miyazaki, MD

Who Should Attend?

The PAGS conference is designed for obstetricians/gynecologists, second, third and fourth-year residents in Ob/Gyn, as well as sub-specialty fellows and advanced practice clinicians. Residents and advanced practice health clinicians are welcome at reduced rates.

ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Global Academy for Medical Education, LLC. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this Live Activity for 20 *AMA PRA Category 1 credits*™ for the conference and (1) 8-hour pre-conference workshops at 8.0 *AMA PRA Category 1 credits*™, (3) 4-hour pre-conference hands-on workshops at 4.0 *AMA PRA Category 1 credits*™ each and (1) post workshop at 3.25 *AMA PRA Category 1 credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

2019

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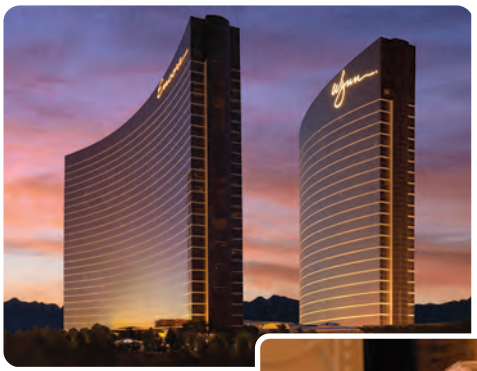

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"LOVE this meeting."

"Excellent topics and presentation was superb"

"Enjoy and appreciated attending as have attended twice. Was straightforward and topics covered very well."

"Thank you for an excellent program!"

"This is such good educational time. I love how there is something current and relevant everytime I attend (this is my third time)."

"Continue with what you do and that is provide 2 ½ days of excellent information to the average practicing Ob/Gyn."

"This is a fantastic conference year after year! I have travelled from Australia on three occasions to attend."

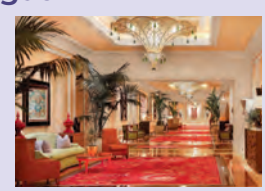
Optional **HANDS-ON WORKSHOPS**
8 CME Credits Available
December 11, 2019

SCIENTIFIC SESSIONS
20 CME Credits Available
December 12-14, 2019

Optional **"P.E.P." PRACTICE MANAGEMENT PROGRAM**
3.25 CME Credits Available
December 14, 2019

About Our Venue

Encore at Wynn Las Vegas



The 2019 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of **just $179* a night for PAGS participants.** To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2019 attendee or reference the block code: 6PAG1219 to receive the discounted rate.

Discount room rate expires November 12, but we urge you to make your arrangements as soon as possible as our room block will sell out.

*Plus $25 amenity fee

How to Register for PAGS

Online: www.PAGS-CME.org
Inquiries: PAGS@globalacademycme.com

	Until Sept 9	Sept 10-Nov 8	After Nov 8
PAGS Scientific Program			
■ Physicians	$795	$895	$995
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■ **Best Buy!** PAGS + P.E.P. Discount Combination Package	$995	$1,195	$1,395
■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future All Day Workshop**	$445	$495	$545
■ **Laparoscopic Suturing Morning Workshop**	$245	$275	$345
■ **Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques**	$245	$275	$345
■ **Vaginal Hysterectomy & Cystourethroscopy Afternoon Workshop**	$325	$350	$395

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 12, 2019. After November 12, 2019 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee, (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

To register and for complete information please see our website: PAGS-cme.org.

Female sexual dysfunction UPDATE

Barbara S. Levy, MD
Dr. Levy is Vice President for Health Policy at the American College of Obstetricians and Gynecologists, Washington, DC.

Sheryl A. Kingsberg, PhD
Dr. Kingsberg is Chief, Division of Behavioral Medicine, Department of Obstetrics and Gynecology, University Hospitals Cleveland Medical Center, and Professor, Departments of Reproductive Biology and Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Dr. Levy reports no financial relationships relevant to this article. Dr. Kingsberg reports that she receives grant or research support from Endoceutics and Palatin Technologies; is a consultant to AMAG, Daré, Duchesnay, Emotional Brain, Endoceutics, IVIX, Lupin, Palatin Technologies, Pfizer, Shionogi, Sprout, SST, and TherapeuticsMD; and is a speaker for TherapeuticsMD.

The recent FDA approval of bremelanotide (Vyleesi) will give clinicians an additional option for treating premenopausal women with HSDD. In this Update, Dr. Barbara Levy explores the drug's efficacy, dosing, and adverse effects with Dr. Sheryl Kingsberg, one of the investigators involved in the bremelanotide clinical trials, and discusses how this medication differs from flibanserin.

Hypoactive sexual desire disorder (HSDD) is the most prevalent sexual health problem in women of all ages, with population-based studies showing that about 36% to 39% of women report low sexual desire, and 8% to 10% meet the diagnostic criteria of low sexual desire and associated distress.[1,2] An expanded definition of HSDD may include[3]:

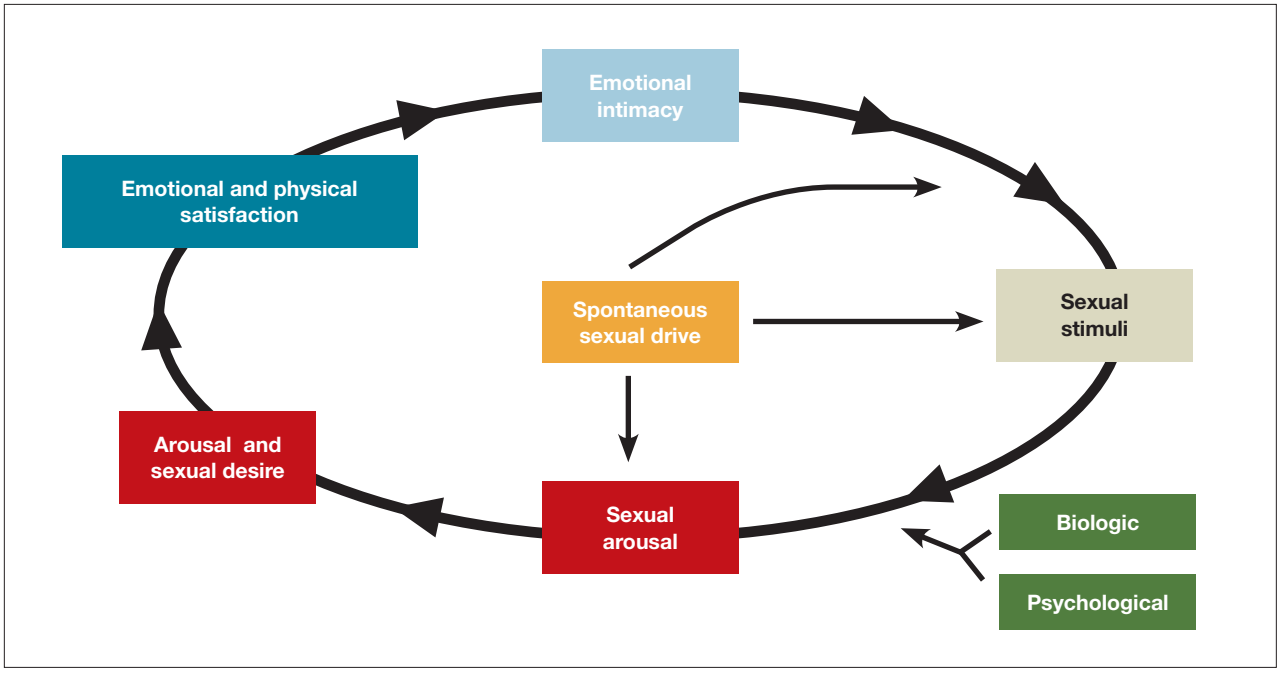
- lack of motivation for sexual activity (reduced or absent spontaneous desire or responsive desire to erotic cues and stimulation; inability to maintain desire or interest through sexual activity)
- loss of desire to initiate or participate in sexual activity (including avoiding situations that could lead to sexual activity) combined with significant personal distress (frustration, loss, sadness, worry) (**FIGURE**).[4]

Despite the high prevalence of HSDD, patients often are uncomfortable and reluctant to voice concerns about low sexual desire to their ObGyn. Further, clinicians may feel ill equipped to diagnose and treat patients with HSDD. ObGyns, however, are well positioned to initiate a general discussion about sexual concerns with patients and use screening tools, such as the Decreased Sexual Desire Screener (DSDS), to facilitate a discussion and clarify a diagnosis of generalized acquired HSDD (**TABLES 1 AND 2**).[5] Helpful guidance on HSDD is available from the American College of Obstetricians and Gynecologists and the International Society for the Study of Women's Sexual Health.[6-8]

Importantly, clinicians have a new

IN THIS ARTICLE

FIGURE Circular model of female sexual response[4]



FAST TRACK

The FDA approved bremelanotide in June 2019 for use in treating acquired, generalized HSDD in premenopausal women

treatment option they can offer to patients with HSDD. Bremelanotide was approved by the US Food and Drug Administration (FDA) on June 21, 2019, to treat acquired, generalized HSDD in premenopausal women. Up until this approval, flibanserin (approved in 2015) was the only drug FDA approved for the treatment of HSDD.

Assessing and treating HSDD today can be likened to managing depression 30 years ago, before selective serotonin receptor inhibitors were available. ObGyns would refer patients with depression to other health care providers, or not even ask patients about depressive symptoms because we had so little to offer. Once safe and effective antidepressants became available, knowing we could provide pharmacologic options made inquiring about depressive symptoms and the use of screening tools more readily incorporated into standard clinical practice. Depression is now recognized as a medical condition with biologic underpinnings, just like HSDD, and treatment options are available for both disorders.

For this Update, I had the opportunity to discuss the clinical trial experience with bremelanotide for HSDD with Dr. Sheryl Kingsberg, including efficacy and safety, dosage and administration, contraindications, and adverse events. She also details an ideal patient for treatment with bremelanotide, and we review pertinent aspects of flibanserin for comparative purposes.

TABLE 1 Validated tools to assess female sexual distress

Validated tool	Assessment area
Decreased Sexual Desire Screener (DSDS)	Brief diagnostic tool for hypoactive sexual desire disorder
Female Sexual Function Index (FSFI)[a]	Desire, arousal, orgasm, and pain
Female Sexual Distress Scale-Revised (FSDS-R)	Distress

[a]FSFI questionnaire and scoring key available at: www.fsfi-questionnaire.com

Bremelanotide: A new therapeutic option

According to the product labeling for bremelanotide, the drug is indicated for the treatment of premenopausal women with acquired, generalized HSDD (low sexual desire that causes marked distress or interpersonal difficulty).[9] This means that the HSDD developed in a woman who previously did not have problems with sexual desire, and that it occurred regardless of the type of stimulation, situation, or partner. In addition, the HSDD should not result from a coexisting medical or psychiatric condition, problems with the relationship, or the effects of a medication or drug substance.

Flibanserin also is indicated for the treatment of premenopausal women with HSDD. While both bremelanotide and flibanserin have indications only for premenopausal women, 2 studies of flibanserin in postmenopausal women have been published.[10,11] Results from these studies in naturally menopausal women suggest that flibanserin may be efficacious in this population, with improvement in sexual desire, reduced distress associated with low desire, and improvement in the number of satisfying sexual events (SSEs).

No trials of bremelanotide in postmenopausal women have been published, but since this drug acts on central nervous system receptors, as does flibanserin, it may have similar effectiveness in postmenopausal women as well.

TABLE 2 Questions included in the Decreased Sexual Desire Screener (DSDS)[5]

The DSDS begins with these 4 yes/no questions:

- In the past, was your level of sexual desire/interest good and satisfying to you?
- Has there been a decrease in your level of sexual desire/interest?
- Are you bothered by your decreased level of sexual desire/interest?
- Would you like your level of sexual desire/interest to increase?

If a woman answers "no" to any of these questions, she is not diagnosed with HSDD

The fifth yes/no multi-part question asks the woman to indicate any factors that may be contributing to her loss of sexual interest. They include:

- An operation, depression, injuries, or other medical condition
- Medications, drugs, or alcohol she is currently taking
- Pregnancy, recent childbirth, menopausal symptoms
- Other sexual issues she may have (pain, decreased arousal or orgasm)
- Her partner's sexual problems
- Dissatisfaction with her relationship or partner
- Stress or fatigue

If a woman answers "no" to all of these items, she can be diagnosed with HSDD

Abbreviation: HSDD, hypoactive sexual desire disorder.

Clinical trials show bremelanotide improves desire, reduces distress

Two phase 3 clinical trials, dubbed the Reconnect studies, demonstrated that, compared with placebo, bremelanotide was associated with statistically significant improvements in sexual desire and levels of distress regarding sexual desire.

The 2 identical, randomized, placebo-controlled multicenter trials included 1,247 premenopausal women with HSDD of at least 6 months' duration.[9,12] Bremelanotide 1.75 mg (or placebo) was self-administered subcutaneously with an autoinjector on an as-desired basis. The 24-week double-blind treatment period was followed by a 52-week open-label extension study.

The co-primary efficacy end points were the change from baseline to end-of-study (week 24 of the double-blind treatment period) in the 1) Female Sexual Function Index (FSFI) desire domain score

and 2) feeling bothered by low sexual desire as measured by Question 13 on the Female Sexual Distress Scale (FSDS). An increase in the FSFI desire domain score over time denotes improvement in sexual desire, while a decrease in the FSDS Question 13 score over time indicates improvement in the level of distress associated with low sexual desire.

In the 2 clinical studies, the mean change from baseline (SD) in the FSFI desire domain score, which ranged from 1.2 to 6.0 at study outset (higher scores indicate greater desire), was:

- study 1: 0.5 (1.1) in the bremelanotide-treated women and 0.2 (1.0) in the placebo-treated women ($P = .0002$)
- study 2: 0.6 (1.0) in the bremelanotide group versus 0.2 (0.9) in the placebo group ($P<.0001$).

For FSDS Question 13, for which the score range was 0 to 4 (higher scores indicate greater bother), the mean change from baseline score was:

- study 1: -0.7 (1.2) in the bremelanotide-treated group compared with -0.4 (1.1) in the placebo-treated group ($P<.0001$)
- study 2: -0.7 (1.1) in the bremelanotide group and -0.4 (1.1) in the placebo group ($P = .0053$).

It should be noted that, in the past, SSEs were used as a primary end point in clinical studies. However, we have shifted from SSEs to desire and distress as an end point because SSEs have little to do with desire. Women worry about and are distressed by the fact that they no longer have sexual appetite. They no longer "want to want" even though their body will be responsive and they can have an orgasm. That is exemplified by the woman in our case scenario (see box, page 18), who very much wants the experience of being able to anticipate with pleasure the idea of having an enjoyable connection with her partner.

Physiologic target: The melanocortin receptor

Bremelanotide's theorized mechanism of action is that it works to rebalance neurotransmitters that are implicated in causing HSDD, acting as an agonist on the melanocortin receptor to promote dopamine release and allow women to perceive sexual cues as rewarding. They can then respond to those cues the way they used to and therefore experience desire. Flibanserin has affinity for serotonin (5-hydroxytryptamine [5-HT]) receptors, with agonist and antagonist activity, as well as moderate antagonist activity on some dopamine receptors.

The bottom line is that we now have treatments to address the underlying biologic aspect of HSDD, which is a biopsychosocial disorder. Again, this has parallels to depression and its biologic mechanism, for which we have effective treatments.

FAST TRACK

Acting as an agonist on the melanocortin receptor to promote dopamine release, bremelanotide allows women to perceive sexual cues as rewarding

Dosing is an as-needed injection

Unlike the daily nighttime oral dose required with flibanserin, bremelanotide is a 1.75-mg dose administered as a subcutaneous injection (in either the thigh or the abdomen) with a pen-like autoinjector, on an as-needed basis. It should be administered at least 45 minutes before anticipated sexual activity. That is a benefit for many women who do not want to take a daily pill when they know that their "desire to desire" may be once per week or once every other week.

Regarding the drug delivery mode, nobody dropped out of the bremelanotide clinical trials because of having to take an injection with an autoinjector, which employs a very thin needle and is virtually painless. A small number of bremelanotide-treated women, about 13%, had injection site reactions (compared with 8% in the placebo

group), which is common with subcutaneous injection. Even in the phase 2 clinical trial, in which a syringe was used to administer the drug, no participants discontinued the study because of the injection mode.

There are no clear pharmacokinetic data on how long bremelanotide's effects last, but it may be anywhere from 8 to 16 hours. Patients should not take more than 1 dose within 24 hours—but since the effect may last up to 16 hours that should not be a problem—and use of more than 8 doses per month is not recommended.

While bremelanotide improves desire, certainly better than placebo, there is also some peripheral improvement in arousal, although women in the trials had only HSDD. We do not know whether bremelanotide would treat arousal disorder, but it will help women with or without arousal difficulties associated with their HSDD, as shown in a subgroup analysis in the trials.[13]

Counsel patients on treatment potentialities

Clinicians should be aware of several precautions with bremelanotide use.

Blood pressure increases. After each dose of bremelanotide, transient increases in blood pressure (6 mm Hg in systolic and 3 mm Hg in diastolic blood pressure) and reductions in heart rate (up to 5 beats per minute) occur; these

Who may benefit from HSDD pharmacotherapy?

The following scenario describes the experience of HSDD in one of Dr. Kingsberg's patients.

CASE Woman avoids sex because of low desire; marriage is suffering

A 40-year-old woman, Sandra, who has been married for 19 years and has fraternal twins aged 8, presented to the behavioral medicine clinic with distressing symptoms of low sexual desire. For several years into the marriage the patient experienced excellent sex drive. After 6 to 7 years, she noticed that her desire had declined and that she was starting to avoid sex. She was irritated when her husband initiated sex, and she would make excuses as to why it was not the right time.

Her husband felt hurt, frustrated, and rejected. The couple was close to divorce because he was angry and resentful. Sandra recognized there was a problem but did not know how to fix it. She could not understand why her interest had waned since she still loved her husband and considered him objectively very attractive.

Sandra came to see Dr. Kingsberg at the behavioral medicine clinic. Using the 5-item validated diagnostic tool called the Decreased Sexual Desire Screener, Dr. Kingsberg diagnosed hypoactive sexual desire disorder (HSDD), a term Sandra had never heard of and did not know was a condition. The patient was relieved to know that she was one of several million women affected by HSDD and that the problem was not just that she was a "bad wife" or that she had some kind of psychological block. She emphasized how much she loved her husband and how she wanted desperately to "want to want desire," as she recalled feeling previously.

Sandra was treated with counseling and psychotherapy in which we addressed the relationship issues, the avoidance of sex, the comfort with being sexual, and the recognition that responsive desire can be helpful (as she was able to have arousal and orgasm and have a satisfying sexual event). The issue was that she had no motivation to seek out sex and had no interest in experiencing that pleasure. In subsequent couple's therapy, the husband recognized that his wife was not intentionally rejecting him, but that she had a real medical condition.

Although Sandra's relationship was now more stable and she and her husband were both working toward finding a solution to Sandra's loss of desire, she was still very distressed by her lack of desire. Sandra tried flibanserin for 3 months but unfortunately did not respond. Sandra heard about the recent approval of bremelanotide and is looking forward to the drug being available so that she can try it.

FAST TRACK

Bremelanotide is not recommended for use in patients at high risk for cardiovascular disease; it is contraindicated in women with uncontrolled hypertension or known cardiovascular disease

measurements return to baseline usually within 12 hours postdose.[9] When you think about whether having sexual desire will increase blood pressure, this may be physiologic. It is similar to walking up a flight of stairs.

The drug is not recommended, however, for use in patients at high risk for cardiovascular disease, and it is contraindicated in women with uncontrolled hypertension or known cardiovascular disease. Blood pressure should be well controlled before bremelanotide is initiated—use of antihypertensive agents is not contraindicated with bremelanotide as the drugs do not interact.

Clinicians are not required to participate in a Risk Evaluation and Mitigation Strategy (REMS) program to prescribe bremelanotide as they are with flibanserin (because of the increased risk of severe hypotension and syncope due to flibanserin's interaction with alcohol).

Drug interactions. Bremelanotide is a melanocortin receptor agonist—a unique compound. Antidepressants, other psychoactive medications, and oral contraceptives are not contraindicated with bremelanotide as there are no known interactions. Alcohol use also is not a contraindication or caution, in contrast to flibanserin. (In April, the FDA issued a labeling change order for flibanserin, specifying that alcohol does not have to be avoided completely when taking flibanserin, but that

women should discontinue drinking alcohol at least 2 hours before taking the drug at bedtime, or skip the flibanserin dose that evening.[14]) Bremelanotide may slow gastric emptying, though, so when a patient is taking oral drugs that require threshold concentrations for efficacy, such as antibiotics, they should avoid bremelanotide. In addition, some drugs, such as indomethacin, may have a delayed onset of action with concomitant bremelanotide use.[9]

Importantly, patients should avoid using bremelanotide if they are taking an oral naltrexone product for treatment of alcohol or opioid addiction, because bremelanotide may decrease systemic exposure of oral naltrexone. That would potentially lead to naltrexone treatment failure and its consequences.[9]

Skin pigmentation changes. Hyperpigmentation occurred with bremelanotide use on the face, gingiva, and breasts, as reported in the clinical trials, in 1% of treated patients who received up to 8 doses per month, compared with no such occurrences in placebo-treated patients. In addition, 38% of patients who received bremelanotide daily for 8 days developed focal hyperpigmentation. It was not confirmed in all patients whether the hyperpigmentation resolved. Women with dark skin were more likely to develop hyperpigmentation.[9]

Common adverse reactions. The most common adverse reactions with bremelanotide treatment are nausea, flushing, injection site reactions, and headache, with most events being mild to moderate in intensity. In the clinical trials, 40% of the bremelanotide-treated women experienced nausea (compared with 1% of placebo-treated women), with most occurrences being mild; for most participants nausea improved with the second dose. Women had nausea that either went away or was intermittent, or it was mild enough that the drug benefits outweighed the tolerability costs—of women who

experienced nausea, 92% continued in the trial, and 8% dropped out because of nausea.[9]

Final considerations

Asking patients about sexual function and using sexual function screening tools can help clinicians identify patients with the decreased sexual desire and associated distress characteristic of HSDD. ObGyns are the appropriate clinicians to treat these women and soon will have 2 pharmacologic options—bremelanotide (anticipated to be available in Fall 2019) and flibanserin—to offer patients with this biopsychosocial disorder that can adversely impact well-being and quality of life. Clinicians should individualize treatment, which may include psychotherapeutic counseling, and counsel patients on appropriate drug use and potential adverse effects.

AMAG Pharmaceuticals, Inc. has announced that they will have a copay assistance program for bremelanotide, where the first prescription of four autoinjectors will be a $0 copay, followed by a $99 copay or less for refills.[15]

FAST TRACK

ObGyns are the appropriate clinicians to treat women with HSDD and soon will have 2 pharmacologic options to offer for this biopsychosocial disorder

References

1. Shifren JL, Monz BU, Russo PA, et al. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol.* 2008;112:970-978.
2. West SL, D'Aloisio AA, Agans RP, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. *Arch Intern Med.* 2008;168:1441-1449.
3. Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions: part II. *J Sex Med.* 2016;13:1888-1906.
4. Basson R. Using a different model for female sexual response to address women's problematic low sexual desire. *J Sex Marital Ther.* 2001;27:395-403.
5. Clayton AH, Goldfischer ER, Goldstein I, et al. Validation of the Decreased Sexual Desire Screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). *J Sex Med.* 2009;6:730-738.
6. American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Gynecology. ACOG practice bulletin no. 213: Female sexual dysfunction. *Obstet Gynecol.* 2019;134:e1-e18.
7. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Mayo Clin Proc.* 2017;92:114-128.
8. Clayton AH, Goldstein I, Kim NN, et al. The International Society for the Study of Women's Sexual Health process of care for management of hypoactive sexual desire disorder in women. *Mayo Clin Proc.* 2018;93:467-487.
9. Vyleesi [package insert]. Waltham, MA: AMAG Pharmaceuticals; 2019.
10. Simon JA, Kingsberg SA, Shumel B, et al. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. *Menopause.* 2014;21;633-640.
11. Portman DJ, Brown L, Yuan, et al. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA study. *J Sex Med.* 2017;14:834-842.
12. Kingsberg SA, Clayton AH, Portman D, et al. Bremelanotide for the treatment of hypoactive sexual desire disorder: two randomized phase 3 trials. *Obstet Gynecol.* Forthcoming.
13. Clayton AH, Lucas J, Jordon R, et al. Efficacy of the Investigational drug bremelanotide in the Reconnect studies. Poster presented at: 30th ECNP Congress of Applied and Translational Neuroscience; September 2-5, 2017, Paris, France.
14. US Food and Drug Administration. FDA orders important safety labeling changes for Addyi [press release]. April 11, 2019. https://www.fda.gov/news-events/press-announcements/fda-orders-important-safety-labeling-changes-addyi. Accessed July 17, 2019.
15. Vyleesi website (https://vyleesipro.com). Accessed August 5, 2019.

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Hormone therapy and cognition: What is best for the midlife brain?

Memory issues are a common source of concern for midlife women. ObGyns are in a unique position to advise women about the roles of menopause and vasomotor symptoms in cognitive function, help normalize the midlife cognitive experience, and help women maintain brain health into late life.

Pauline M. Maki, PhD

IN THIS ARTICLE

CASE HT for vasomotor symptoms in perimenopausal woman with cognitive concerns

Jackie is a 49-year-old woman. Her body mass index is 33 kg/m^2, and she has mild hypertension that is effectively controlled with antihypertensive medications. Otherwise, she is in good health.

During her annual gynecologic exam, she reports that for the past 9 months her menstrual cycles have not been as regular as they used to be and that 3 months ago she skipped a cycle. She is having bothersome vasomotor symptoms (VMS) and is concerned about her memory. She says she is forgetful at work and in social situations. During a recent presentation, she could not remember the name of one of her former clients. At a work happy hour, she forgot the name of her coworker's husband, although she did remember it later after returning home.

Her mother has Alzheimer disease (AD), and Jackie worries about whether she, too, might be developing dementia and whether her memory will fail her in social situations.

She is concerned about using hormone therapy (HT) for her vasomotor symptoms because she has heard that it can lead to breast cancer and/or AD.

How would you advise her?

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The author reports no financial relationships relevant to this article.

HT remains the most effective treatment for bothersome VMS, but concerns about its cognitive safety persist. Such concerns, and indeed a black-box warning about the risk of dementia with HT use, initially arose following the 2003 publication of the Women's Health Initiative Memory Study (WHIMS), a randomized, placebo-controlled trial of HT for the primary prevention of dementia in women aged 65 years and older at baseline.[1] The study found that combination estrogen/progestin therapy was associated with a 2-fold increase in dementia when compared with placebo.

One of the critical questions arising even before WHIMS was whether the cognitive risks associated with HT that were seen in WHIMS apply to younger women. Attempting to answer the question and adding fuel to the fire are the results of a recent case-control study from Finland.[2] This study compared HT use in Finnish women with and

without AD and found that HT use was higher among Finnish women with AD compared with those without AD, regardless of age. The authors concluded, "Our data must be implemented into information for the present and future users of HT, even though the absolute risk increase is small."

However, given the limitations inherent to observational and registry studies, and the contrasting findings of 3 high-quality, randomized controlled trials (RCTs; more details below), providers actually can reassure younger peri- and postmenopausal women about the cognitive safety of HT.[3] They also can explain to patients that cognitive symptoms like the ones described in the case example are normal and provide general guidance to midlife women on how to optimize brain health.

Closer look at WHI and RCT research pinpoints cognitively neutral HT

In WHIMS, the combination of conjugated equine estrogen (CEE; 0.625 mg/d) plus medroxyprogesterone acetate (MPA; 2.5 mg/d) led to a doubling of the risk of all-cause dementia compared with placebo in a sample of 4,532 women aged 65 years and older at baseline.[1] CEE alone (0.625 mg) did not lead to an increased risk of all-cause dementia.[4]

Whether those formulations led to cognitive impairment in younger postmenopausal women was the focus of WHIMS-Younger (WHIMS-Y), which involved WHI participants aged 50 to 55 years at baseline.[5] Results revealed neutral cognitive effects (ie, no differences in cognitive performance in women randomly assigned to HT or placebo) in women tested 7.2 years after the end of the WHI trial. WHIMS-Y findings indicated that there were no sustained cognitive risks of CEE or CEE/MPA therapy. Two randomized, placebo-controlled trials involving younger postmenopausal women yielded similar findings.[6,7] HT shown to produce cognitively neutral effects during active treatment included transdermal estradiol plus micronized progesterone,[6] CEE plus progesterone,[6] and oral estradiol plus vaginal progesterone gel.[7] The findings of these randomized trials are critical for guiding decisions regarding

FAST TRACK

Although a recent case-control study found that HT use was higher among women with AD, RCT data reassure younger peri- and postmenopausal women about the cognitive safety of HT

ILLUSTRATION: MARY ELLEN NIATAS FOR OBG MANAGEMENT

TABLE 1 Hormone therapy formulations shown to produce cognitively neutral effects in early postmenopausal women

- Transdermal estradiol (50 µg/wk) plus micronized progesterone (200 mg, 12 d/month)
- Oral conjugated equine estrogen (0.45 mg) plus micronized progesterone (200 mg, 12 d/month)
- Oral estradiol (1 mg/d) plus vaginal progesterone gel (10 d/month)

the cognitive risks of HT in early postmenopausal women (**TABLE 1**).

What about women with VMS?

A key gap in knowledge about the cognitive effects of HT is whether HT confers cognitive advantages to women with bothersome VMS. This is a striking absence given that the key indication for HT is the treatment of VMS. While some symptomatic women were included in the trials of HT in younger postmenopausal women described above, no large trial to date has selectively enrolled women with moderate-to-severe VMS to determine if HT is cognitively neutral, beneficial, or detrimental in that group. Some studies involving midlife women have found associations between VMS (as measured with ambulatory skin conductance monitors) and multiple measures of brain health, including memory performance,[8] small ischemic lesions on structural brain scans,[9] and altered brain function.[10] In a small trial of a nonhormonal intervention for VMS, improvement in VMS following the intervention was directly related to improvement in memory performance.[11] The reliability of these findings continues to be evaluated but raises the hypothesis that VMS treatments might improve memory in midlife women.

FAST TRACK

The hypothesis that treatment of VMS might improve memory in midlife women cannot be reliably proven with currently published data

Memory complaints common among midlife women

About 60% of women report an undesirable change in memory performance at midlife as compared with earlier in their lives.[12,13] Complaints of forgetfulness are higher in perimenopausal and postmenopausal women compared with premenopausal women, even when those women are similar in age.[14] Two large prospective studies found that memory performance decreases during the perimenopause and then rebounds, suggesting a transient decrease in memory.[15,16] Although cognitive complaints are common among women in their 40s and 50s, AD is rare in that age group. The risk is largely limited to those women with a parent who developed dementia before age 65, as such cases suggest a familial form of AD.

What causes cognitive difficulties during midlife?

First, some cognitive decline is expected at midlife based on increasing age. Second, above and beyond the role of chronologic aging (ie, getting one year older each year), ovarian aging plays a role. A role of estrogen was verified in clinical trials showing that memory decreased following oophorectomy in premenopausal women in their 40s but returned to presurgical levels following treatment with estrogen therapy (ET).[17] Cohort studies indicate that women who undergo oophorectomy before the typical age of menopause are at increased risk for cognitive impairment or dementia, but those who take ET after oophorectomy until the typical age of menopause do not show that risk.[18]

Third, cognitive problems are linked not only to VMS but also to sleep disturbance, depressed mood, and increased anxiety—all of which are common in midlife women.[15,19] Lastly, health factors play a role. Hypertension, obesity, insulin resistance, diabetes, and smoking are associated with adverse brain changes at midlife.[20]

Giving advice to your patients

First, normalize the cognitive complaints, noting that some cognitive changes are an expected part of aging for all people regardless of whether they are male or female. Advise that while the best studies indicate that these cognitive lapses are especially common in perimenopausal women, they

CONTINUED ON PAGE 26

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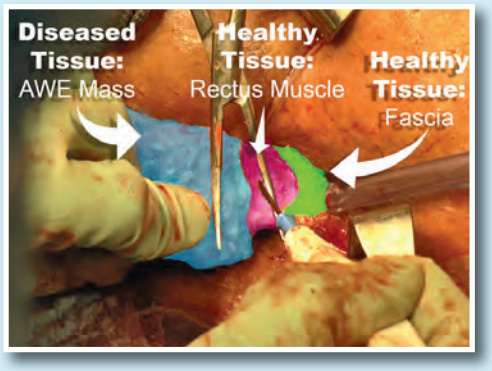

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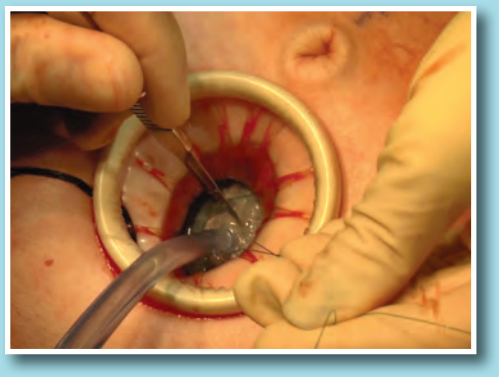

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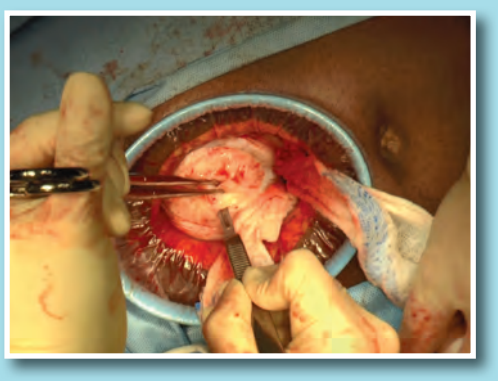

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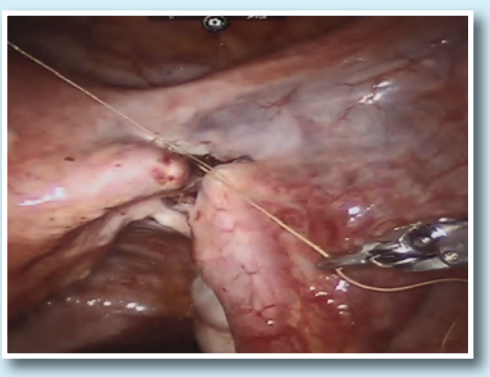

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CONTINUED FROM PAGE 24

TABLE 2 Patient Health Questionnaire (PHQ)-2

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

- A score ≥ 3 indicates probable major depressive disorder.
- Patients who screen positive should be further evaluated with the PHQ-9 or other screening instruments to determine whether they meet criteria for a depressive disorder.
- Welcome to the Patient Health Questionnaire (PHQ) Screeners. Screener overview. http://www.phqscreeners.com/select-screener/36. Accessed June 28, 2019.

FAST TRACK

Patients can keep their brains healthy by treating hypertension, reducing BMI, engaging in regular aerobic exercise, eating a Mediterranean diet, maintaining an active social life, and engaging in novel challenging activities

appear to be temporary; women are likely to resume normal cognitive function once the hormonal changes associated with menopause subside.[15,16] Note that the one unknown is the role that VMS play in memory problems and that some studies indicate a link between VMS and cognitive problems. Women may experience some cognitive improvement if VMS are effectively treated.

Advise patients that the Endocrine Society, the North American Menopause Society (NAMS), and the International Menopause Society all have published guidelines saying that the benefits of HT outweigh the risks for most women aged 50 to 60 years.[21] For concerns about the cognitive adverse effects of HT, discuss the best quality evidence—that which comes from randomized trials—which shows no harmful effects of HT in midlife women.[5-7] Especially reassuring is that one of these high-quality studies was conducted by the same researchers who found that HT can be risky in older women (ie, the WHI Investigators).[5]

Going one step further: Protecting brain health

As primary care providers to midlife women, ObGyns can go one step further and advise patients on how to proactively nurture their brain health. Great evidence-based resources for information on maintaining brain health include the Alzheimer's Association (https://www.alz.org) and the Women's Brain Health Initiative (https://womensbrainhealth.org). Primary prevention of AD begins decades before the typical age of an AD diagnosis, and many risk factors for AD are modifiable.[22] Patients can keep their brains healthy through myriad approaches including treating hypertension, reducing body mass index, engaging in regular aerobic exercise (brisk walking is fine), eating a Mediterranean diet, maintaining an active social life, and engaging in novel challenging activities like learning a new language or a new skill like dancing.[20]

Also important is the overlap between cognitive issues, mood, and alcohol use. In the opening case, Jackie mentions alcohol use and social withdrawal. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), low-risk drinking for women is defined as no more than 3 drinks on any single day and no more than 7 drinks per week.[23] Heavy alcohol use not only affects brain function but also mood, and depressed mood can lead women to drink excessively.[24]

In addition, Jackie's mother has AD, and that stressor can contribute to depressed feelings, especially if Jackie is involved in caregiving. A quick screen for depression with an instrument like the Patient Health Questionnaire-2 (PHQ-2; **TABLE 2**)[25] can rule out a more serious mood disorder—an approach that is particularly important for patients with a history of major depression, as 58% of those patients experience a major depressive episode during the menopausal transition.[26] For this reason, it is important to ask patients like Jackie if they have a history of depression; if they do and were treated

medically, consider prescribing the antidepressant that worked in the past. For information on menopause and mood-related issues, providers can access new guidelines from NAMS and the National Network of Depression Centers (NNDC).[27] There is also a handy patient information sheet to accompany those guidelines on the NAMS website (https://www.menopause.org/docs/default-document-library/menonote-menopause-and-depression.pdf).

CASE Resolved

When approaching Jackie, most importantly, I would normalize her experience and tell her that memory problems are common in the menopausal transition, especially for women with bothersome VMS. Research suggests that the memory problems she is experiencing are related to hormonal changes and not to AD, and that her memory will likely improve once she has transitioned through the menopause. I would tell her that AD is rare at midlife unless there is a family history of early onset of AD (before age 65), and I would verify the age at which her mother was diagnosed to confirm that it was late-onset AD.

For now, I would recommend that she be prescribed HT for her bothersome hot flashes using one of the "safe" formulations in the Table on page 24. I also would tell her that there is much she can do to lower her risk of AD and that it is best to start now as she enters her 50s because that is when AD changes typically start in the brain, and she can start to prevent those changes now.

I would tell her that experts in the field of AD agree that these lifestyle interventions are currently the best way to prevent AD and that the more of them she engages in, the more her brain will benefit. I would advise her to continue to manage her hypertension and to consider ways of lowering her BMI to enhance her brain health. Engaging in regular brisk walking or other aerobic exercise, as well as incorporating more of the Mediterranean diet into her daily food intake would also benefit her brain. As a working woman, she is exercising her brain, and she should consider other cognitively challenging activities to keep her brain in good shape.

I would follow up with her in a few months to see if her memory functioning is better. If it is not, and if her VMS continue to be bothersome, I would increase her dose of HT. Only if her VMS are treated but her memory problems are getting worse would I screen her with a Mini-Mental State Exam and refer her to a neurologist for an evaluation. ●

References

1. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2651-2662.
2. Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. *BMJ*. 2019;364:1665.
3. Maki PM, Girard LM, Manson JE. Menopausal hormone therapy and cognition. *BMJ*. 2019;364:1877.
4. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947-2958.
5. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med*. 2013;173:1429-1436.
6. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. *PLoS Med*. 2015;12:e1001833.
7. Henderson VW, St. John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. *Neurology*. 2016;87:699-708.
8. Maki PM, Drogos LL, Rubin LH, et al. Objective hot flashes are negatively related to verbal memory performance in midlife women. *Menopause*. 2008;15:848-856.
9. Thurston RC, Aizenstein HJ, Derby CA, et al. Menopausal hot flashes and white matter hyperintensities. *Menopause*. 2016;23:27-32.
10. Thurston RC, Maki PM, Derby CA, et al. Menopausal hot flashes and the default mode network. *Fertil Steril*. 2015;103:1572-1578.e1.
11. Maki PM, Rubin LH, Savarese A, et al. Stellate ganglion blockade and verbal memory in midlife women: evidence from a randomized trial. *Maturitas*. 2016;92:123-129.
12. Woods NF, Mitchell ES, Adams C. Memory functioning among midlife women: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2000;7:257-265.
13. Sullivan Mitchell E, Fugate Woods N. Midlife women's attributions about perceived memory changes: observations from the Seattle Midlife Women's Health Study. *J Womens Health Gend Based Med*. 2001;10:351-362.
14. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. *Am J Epidemiol*. 2000;152:463-473.
15. Greendale GA, Wight RG, Karlamangia AS, et al. Menopause-

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Morcellation use in gynecologic surgery: Current clinical recommendations and cautions

Here, evolving thought on preoperative evaluation and counseling, updated ACOG guidelines, and changes implemented at the authors' institution

Jessica G. Putman, MD; Abigail S. Zamorano, MD, MPHS; and David G. Mutch, MD

Morcellation of gynecologic surgical specimens became controversial after concerns arose about the potential for inadvertent spread of malignant cells throughout the abdomen and pelvis during tissue morcellation of suspected benign disease. In 2014, the US Food and Drug Administration (FDA) issued a warning against the use of laparoscopic power morcellation specifically for myomectomy or hysterectomy in the treatment of leiomyomas (fibroids) because of the risk of spreading undiagnosed malignancy throughout the abdomen and pelvis.[1] This warning was issued after a high-profile case occurred in Boston in which an occult uterine sarcoma was morcellated during a supracervical robot-assisted hysterectomy for suspected benign fibroids.

Recently, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion with updated recommendations for practice detailing the risks associated with morcellation and suggestions for patient counseling regarding morcellation.[2]

In this review, we summarize the techniques and risks of morcellation, the epidemiology of undiagnosed uterine malignancies, practice changes noted at our institution, and clinical recommendations moving forward. A case scenario illustrates keys steps in preoperative evaluation and counseling.

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Dr. Mutch reports that he receives grant or research support from the National Institutes of Health and the GOG Foundation and that he is a consultant and speaker for Clovis and AstraZeneca. Dr. Putman and Dr. Zamorano report no financial relationships relevant to this article.

Morcellation uses—and risks

Morcellation is the surgical process of dividing a large tissue specimen into smaller pieces to facilitate their removal through the small incisions made in minimally invasive

IN THIS ARTICLE

surgery. Morcellation may be performed with a power instrument or manually.

In power morcellation, an electromechanical instrument is used to cut or shave the specimen; in manual morcellation, the surgeon uses a knife to carve the specimen. Power morcellation is performed through a laparoscopic incision, while the manual technique is performed through a minilaparotomy or vaginally after hysterectomy (**TABLE**). Unlike uncontained morcellation, contained morcellation involves the use of a laparoscopic bag to hold the specimen and therefore prevent tissue dissemination in the abdomen and pelvis.

Morcellation has greatly expanded our ability to perform minimally invasive surgery—for example, in patients with specimens that cannot be extracted en bloc through the vagina after hysterectomy or, in the case of myomectomy or supracervical hysterectomy without a colpotomy, through small laparoscopic ports. Minimally invasive surgery improves patient care, as it is associated with lower rates of infection, blood loss, venous thromboembolism, wound and bowel complications, postoperative pain, and shorter overall recovery time and hospital stay versus traditional open surgery.[3,4] Furthermore, laparoscopic hysterectomy has a 3-fold lower risk of mortality compared with open hysterectomy.[4] For these reasons, ACOG recommends choosing a minimally invasive approach for all benign hysterectomies whenever feasible.[3]

With abundant data supporting the use of a minimally invasive approach, laparoscopic morcellation allowed procedures involving larger tissue specimens to be accomplished without the addition of a minilaparotomy for tissue extraction. However, disseminating potentially malignant tissue throughout the abdomen and pelvis during the morcellation process remains a risk. While tissue spread can occur with either power or manual morcellation, the case that drew media attention to the controversy used power morcellation, and thus intense scrutiny focused on this technique. Morcellation has additional risks, including direct injury to surrounding organs, disruption of the pathologic specimen, and distribution of benign tissue throughout the abdomen and pelvis, such as fibroid, endometriosis, and adenomyosis implants.[5-7]

FAST TRACK

Morcellation has greatly expanded our ability to perform minimally invasive surgery, such as in patients with specimens that cannot be extracted en bloc through the vagina after hysterectomy

TABLE Approaches to morcellation

Type of morcellation	Method
Power, contained	Laparoscopic incisions (umbilical or suprapubic)
Manual, uncontained	Vaginally
Manual, contained	Minilaparotomy or Vaginally

The challenge of leiomyosarcoma

The primary controversy surrounding morcellation of fibroid tissue specimens is the potential for undiagnosed malignancy, namely uterine leiomyosarcoma or endometrial stromal sarcoma. While other gynecologic malignancies, including cervical and endometrial cancers, are more common and potentially could be disseminated by morcellation, these cancers are more reliably diagnosed preoperatively with cervical and endometrial biopsies, and they do not tend to mimic benign diseases.

Epidemiology and risk factors. Uterine leiomyosarcoma is rare, with an estimated incidence of 0.36 per 100,000 woman-years.[8] However, leiomyosarcoma can mimic the appearance and clinical course of benign fibroids, making preoperative diagnosis difficult. Risk factors for leiomyosarcoma include postmenopausal status, with a median age of 54 years at diagnosis, tamoxifen use longer than 5 years, black race, history of pelvic radiation, and certain hereditary cancer syndromes, such as Lynch syndrome.[9-11] Because of these risk factors, preoperative evaluation is crucial to determine the most appropriate surgical method for removal of a large, fibroid uterus (see "Employ shared decision making" on page 32).

Estimated incidence at benign hysterectomy. The incidence of leiomyosarcoma diagnosed at the time of benign hysterectomy or myomectomy has been studied extensively since the FDA's 2014 warning was released, with varying rates identified.[11,12] The FDA's analysis cited a risk of 1 in 498 for unsuspected leiomyosarcoma and 1 in 352 for uterine sarcoma.[1] Notably, this analysis excluded studies of women undergoing surgery for presumed fibroids in which no leiomyosarcoma was found on pathology, likely inflating the quoted prevalence. The FDA and other entities subsequently performed further analyses, but a systematic literature review and meta-analysis by the Agency for Healthcare Research and Quality (AHRQ) in 2017 is probably the most accurate. That review included 160 studies and reported a prevalence of less than 1 in 10,000 to 1 in 770, lower than the FDA-cited rate.[13]

Prognosis. The overall prognosis for women with leiomyosarcoma is poor. Studies indicate a 5-year survival rate of only 55.4%, even in stage 1 disease that is apparently confined to the uterus.[9] Although evidence is limited linking morcellation to increased recurrence of leiomyosarcoma, data from small, single-center, retrospective studies cite a worse prognosis, higher risk of recurrence, and shorter progression-free survival after sarcoma morcellation compared with patients who underwent en bloc resection.[12,14] Of note, these studies evaluated patients who underwent uncontained morcellation of specimens with unsuspected leiomyosarcoma.

CASE Woman with enlarged, irregular uterus and heavy bleeding

A 40-year-old woman (G2P2) with a history of 2 uncomplicated vaginal deliveries presents for evaluation of heavy uterine bleeding. She has regular periods, every 28 days, and she bleeds for 7 days, saturating 6 pads per day. She is currently taking only oral iron therapy as recommended by her primary care physician. Over the last 1 to 2 years she has felt that her abdomen has been getting larger and that her pants do not fit as well. She is otherwise in excellent health, exercises regularly, and has a full-time job. She has not been sexually active in several months.

The patient's vitals are within normal limits and her body mass index (BMI) is 35 kg/m^2. Pelvic examination reveals that she has an enlarged, irregular uterus with the fundus at the level of the umbilicus. The exam is otherwise unremarkable. On further questioning, the patient does not desire future fertility.

What next steps would you include in this patient's workup, including imaging studies or lab tests? What surgical options would you give her? How would your management differ if this patient were 70 years old (postmenopausal)?

Perform a thorough preoperative evaluation to optimize outcomes

Women like this case patient who present with symptoms that may lead to treatment with myomectomy or hysterectomy should undergo appropriate preoperative testing to evaluate for malignancy.

According to ACOG guidance, patients should undergo a preoperative endometrial biopsy if they[15]:

- are older than 45 years with abnormal uterine bleeding
- are younger than 45 years with unopposed estrogen exposure (including obesity or polycystic ovary syndrome)
- have persistent bleeding, or
- failed medical management.

Our case patient is younger than 45 but is obese (BMI, 35) and therefore is a candidate for endometrial biopsy. Additionally, all patients should have up-to-date cervical cancer screening. ACOG also recommends appropriate use of imaging with ultrasonography or magnetic resonance imaging (MRI), although imaging is not recommended solely to evaluate for malignancy, as it cannot rule out the diagnosis of many gynecologic malignancies, including leiomyosarcoma.[2]

Currently, no tests are available to completely exclude a preoperative diagnosis of leiomyosarcoma. While studies have

FAST TRACK

Currently, no tests are available to completely exclude a preoperative diagnosis of leiomyosarcoma

evaluated the use of MRI combined with lactate dehydrogenase isoenzyme testing, the evidence is weak, and this method is not recommended. Sarcoma is detected by endometrial sampling only 30% to 60% of the time, but it should be performed if the patient meets criteria for sampling or if she has other risk factors for malignancy.[16] There are no data to support biopsy of presumed benign fibroids prior to surgical intervention. Patients should be evaluated with a careful history and physical examination for other uterine sarcoma risk factors.

Employ shared decision making

Clinicians should use shared decision making with patients to facilitate decisions on morcellation use in gynecologic surgeries for suspected benign fibroids. Informed consent must be obtained after thorough discussion and counseling regarding the literature on morcellation.[17] For all patients, including the case patient described, this discussion should include alternative treatment options, surgical approach with associated risks, the use of morcellation, the incidence of leiomyosarcoma with presumed benign fibroids, leiomyosarcoma prognosis, and the risk of disseminating benign or undiagnosed cancerous tissue throughout the abdomen and pelvis.

Some would argue that the risks of laparotomy outweigh the possible risks associated with morcellation during a minimally invasive myomectomy or hysterectomy. However, this risk analysis is not uniform across all patients, and it is likely that in older women, because they have an a priori increased risk of malignancy in general, including leiomyosarcoma, the risks of power morcellation may outweigh the risks of open surgery.[18] Younger women have a much lower risk of leiomyosarcoma, and thus discussion and consideration of the patient's age should be a part of counseling. If the case patient described was 70 years of age, power morcellation might not be recommended, but these decisions require an in-depth discussion with the patient to make an informed decision and ensure patient autonomy.

FAST TRACK

Use shared decision making with patients to facilitate decisions on morcellator use in gynecologic surgery for suspected benign fibroids

The contained morcellation approach

Many surgeons who perform minimally invasive procedures use contained morcellation. In this approach, specimens are placed in a containment bag and morcellated with either power instruments or manually to ensure no dissemination of tissue. Manual contained morcellation can be done through a minilaparotomy or the vagina, depending on the procedure performed, while power contained morcellation is performed through a 15-mm laparoscopic incision.

Currently, one containment bag has been FDA approved for use in laparoscopic contained power morcellation.[19] Use of a containment bag increases operative time by approximately 20 minutes, due to the additional steps required to accomplish the procedure.[20] Its use, however, suggests a decrease in the risk of possible disease spread and it is feasible with appropriate surgeon training.

One study demonstrated the safety and feasibility of power morcellation within an insufflated containment bag, and subsequent follow-up revealed negative intraperitoneal washings.[21,22] In another study evaluating tissue dissemination with contained morcellation of tissue stained with dye, the authors noted actual spillage of tissue fragments in only one case.[23] Although more information is needed to confirm prevention of tissue dissemination and the safety of contained tissue morcellation, these studies provide promising data supporting the use of tissue morcellation in appropriate cases in order to perform minimally invasive surgery with larger specimens.

CASE Next steps and treatment outcome

The patient has up-to-date and negative cervical cancer screening. The complete blood count is notable for a hemoglobin level of 11.0 g/dL (normal range, 12.1 to 15.1 g/dL). You perform an endometrial biopsy; results are negative for malignancy. You order pelvic ultrasonography to better characterize the location and size of the fibroids. It shows multiple leiomyomas throughout the myometrium, with the 2 largest fibroids (measuring 5 and 7 cm) located in

the left anterior and right posterolateral aspects of the uterus, respectively. Several 3- to 4-cm fibroids appear to be disrupting the endometrial canal, and there is no evidence of an endometrial polyp. There do not appear to be any cervical or lower uterine segment fibroids, which may have further complicated the proposed surgery.

You discuss treatment options for abnormal uterine bleeding with the patient, including initiation of combined oral contraceptive pills, placement of a levonorgestrel-containing intrauterine device, endometrial ablation, uterine artery embolization, and hysterectomy. You discuss the risks and benefits of each approach, keeping in mind the fibroids that are disrupting the contour of the endometrial canal and causing her bulk symptoms.

The patient ultimately decides to undergo a hysterectomy and would like it to be performed with a minimally invasive procedure, if possible. Because of the size of her uterus, you discuss the use of contained power morcellation, including the risks and benefits. You have a thorough discussion about the risk of occult malignancy, although she is at lower risk because of her age, and she consents.

The patient undergoes an uncomplicated total laparoscopic hysterectomy with bilateral salpingectomy. The specimen is removed using contained power morcellation through the umbilical port site. She has an unremarkable immediate postoperative course and is discharged on postoperative Day 1.

You see the patient in the clinic 2 weeks later. She reports minimal pain or discomfort and has no other complaints. Her abdominal incisions are healing well. You review the final pathology report with her, which showed no evidence of malignancy.

Society guidance on clinical applications

In current clinical practice, many surgeons have converted to exclusively performing contained morcellation in appropriate patients with a low risk of uterine leiomyosarcoma. At our institution, uncontained morcellation has not been performed since the FDA's 2014 warning.

ACOG and AAGL (formerly the American

Association of Gynecologic Laparoscopists) recommend use of containment bags as a solution to continue minimally invasive surgery for large specimens without the risk of possible tissue dissemination, although more in-depth surgeon training is likely required for accurate technique.[2,24] The Society of Gynecologic Oncology (SGO) states that power morcellation or any other techniques that divide the uterus in the abdomen are contraindicated in patients with documented or highly suspected malignancy.[25]

With the presented data of risks associated with uncontained morcellation and agreement of the ACOG, AAGL, and SGO professional societies, **we recommend that all morcellation be performed in a contained fashion to prevent the dissemination of benign or undiagnosed malignant tissue throughout the abdomen and pelvis.** Shared decision making and counseling on the risks, benefits, and alternatives are paramount for patients to make informed decisions about their medical care. Continued exploration of techniques and methods for safe tissue extraction is still needed to improve minimally invasive surgical options for all women. ●

FAST TRACK

Along with ACOG, AAGL, and SGO, we recommend that all morcellation be performed in a contained fashion to prevent dissemination of undiagnosed malignant tissue throughout the abdomen and pelvis

References

1. US Food and Drug Administration. Updated: Laparoscopic uterine power morcellation in hysterectomy and myomectomy: FDA safety communication. November 24, 2014; updated April 7, 2016. https://wayback.archive-it.org/7993/20170404182209/https:/www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm. Accessed July 23, 2019.
2. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG committee opinion no. 770: Uterine morcellation for presumed leiomyomas. *Obstet Gynecol.* 2019;133:e238-e248.
3. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG committee opinion no. 701: Choosing the route of hysterectomy for benign disease. *Obstet Gynecol.* 2017;129:1149-1150.
4. Wiser A, Holcroft CA, Tolandi T, et al. Abdominal versus laparoscopic hysterectomies for benign diseases: evaluation of morbidity and mortality among 465,798 cases. *Gynecol Surg.* 2013;10:117-122.
5. Winner B, Biest S. Uterine morcellation: fact and fiction surrounding the recent controversy. *Mo Med.* 2017;114:176-180.
6. Tulandi T, Leung A, Jan N. Nonmalignant sequelae of unconfined morcellation at laparoscopic hysterectomy or myomectomy. *J Minim Invasive Gynecol.* 2016;23:331-337.
7. Milad MP, Milad EA. Laparoscopic morcellator-related complications. *J Minim Invasive Gynecol.* 2014;21:486-491.
8. Toro JR, Travis LB, Wu HJ, et al. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the Surveillance, Epidemiology and End Results program, 1978-2001: an analysis of 26,758 cases. *Int J Cancer.* 2006;119:2922-2930.
9. Seagle BL, Sobecki-Rausch J, Strohl AE, et al. Prognosis and treatment of uterine leiomyosarcoma: a National Cancer Database study. *Gynecol Oncol.* 2017;145:61-70.
10. Ricci S, Stone RL, Fader AN. Uterine leiomyosarcoma: epidemiology, contemporary treatment strategies and the impact of uterine morcellation. *Gynecol Oncol.* 2017;145:208-216.
11. Leibsohn S, d'Ablaing G, Mishell DR Jr, et al. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. *Am J Obstet Gynecol.* 1990;162:968-974. Discussion 974-976.
12. Rowland M, Lesnock J, Edwards R, et al. Occult uterine cancer in patients undergoing laparoscopic hysterectomy with morcellation [abstract]. *Gynecol Oncol.* 2012;127:S29.
13. Hartmann KE, Fonnesbeck C, Surawicz T, et al. Management of uterine fibroids. Comparative effectiveness review no. 195. AHRQ Publication No. 17(18)-EHC028-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2017. https://effectivehealthcare.ahrq.gov/topics/uterine-fibroids/research-2017. Accessed July 23, 2019.
14. Pritts EA, Parker WH, Brown J, et al. Outcome of occult uterine leiomyosarcoma after surgery for presumed uterine fibroids: a systematic review. *J Minim Invasive Gynecol.* 2015;22:26-33.
15. American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Gynecology. Practice bulletin no. 128: Diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol.* 2012;120:197-206.
16. Bansal N, Herzog TJ, Burke W, et al. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. *Gynecol Oncol.* 2008 Jul;110(1):43–48.
17. American College of Obstetricians and Gynecologists Committee on Ethics. ACOG committee opinion no. 439: Informed consent. *Obstet Gynecol.* 2009;114:401-408.
18. Wright JD, Cui RR, Wang A, et al. Economic and survival implications of use of electric power morcellation for hysterectomy for presumed benign gynecologic disease. *J Natl Cancer Inst.* 2015;107:djv251.
19. US Food and Drug Administration. FDA allows marketing of first-of-kind tissue containment system for use with certain laparoscopic power morcellators in select patients [press release]. April 7, 2016. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494650.htm. Accessed July 23, 2019.
20. Winner B, Porter A, Velloze S, et al. S. Uncontained compared with contained power morcellation in total laparoscopic hysterectomy. *Obstet Gynecol.* 2015 Oct;126(4):834–8.
21. Cohen SL, Einarsson JI, Wang KC, et al. Contained power morcellation within an insufflated isolation bag. *Obstet Gynecol.* 2014;124:491-497.
22. Cohen SL, Greenberg JA, Wang KC, et al. Risk of leakage and tissue dissemination with various contained tissue extraction (CTE) techniques: an in vitro pilot study. *J Minim Invasive Gynecol.* 2014;21:935-939.
23. Cohen SL, Morris SN, Brown DN, et al. Contained tissue extraction using power morcellation: prospective evaluation of leakage parameters. *Am J Obstet Gynecol.* 2016;214(2):257.e1-257.e6.
24. AAGL. AAGL practice report: morcellation during uterine tissue extraction. *J Minim Invasive Gynecol.* 2014;21:517-530.
25. Society of Gynecologic Oncology. Position statement: morcellation. 2013. https://www.sgo.org/newsroom/position-statements-2/morcellation/.Accessed July 23, 2019.

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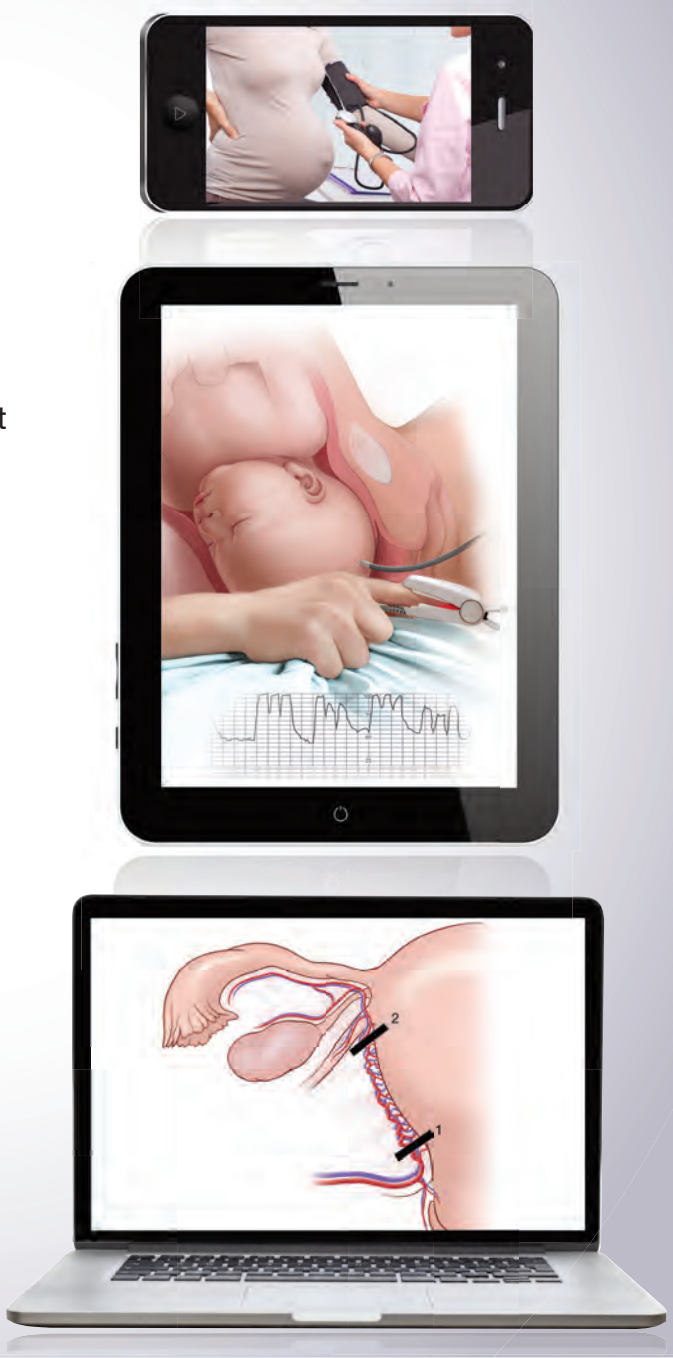

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Hysteroscopic removal of adenocarcinoma (concomitant with a benign polyp) in a postmenopausal woman with abnormal uterine bleeding.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Office hysteroscopic evaluation of postmenopausal bleeding

Postmenopausal bleeding can indicate endometrial carcinoma. When and how can hysteroscopy make the difference in diagnosis (and operative intervention)?

Amy L. Garcia, MD

Postmenopausal bleeding (PMB) is the presenting sign in most cases of endometrial carcinoma. Prompt evaluation of PMB can exclude, or diagnose, endometrial carcinoma.[1] Although no general consensus exists for PMB evaluation, it involves endometrial assessment with transvaginal ultrasonography (TVUS) and subsequent endometrial biopsy when a thickened endometrium is found. When biopsy results reveal insufficient or scant tissue, further investigation into the etiology of PMB should include office hysteroscopy with possible directed biopsy. In this article I discuss the prevalence of PMB and steps for evaluation, providing clinical takeaways.

Postmenopausal bleeding: Its risk for cancer

Abnormal uterine bleeding (AUB) in a postmenopausal woman is of particular concern to the gynecologist and the patient because of the increased possibility of endometrial carcinoma in this age group. AUB is present in more than 90% of postmenopausal women with endometrial carcinoma, which leads to diagnosis in the early stages of the disease. Approximately 3% to 7% of postmenopausal women with PMB will have endometrial carcinoma.[2] Most women with PMB, however, experience bleeding secondary to atrophic changes of the vagina or endometrium and not to endometrial carcinoma. (**FIGURE 1,** page 38**; VIDEO 1**) In addition, women who take gonadal steroids for hormone replacement therapy (HRT) may experience breakthrough bleeding that leads to initial investigation with TVUS.

The risk of malignancy in polyps in postmenopausal women over the age of 59 who present with PMB is approximately 12%, and hysteroscopic resection should routinely be performed. For asymptomatic patients, the risk of a malignant lesion is low—approximately 3%—and for these women intervention should be assessed individually for the risks of carcinoma and benefits of hysteroscopic removal.[3]

Clinical takeaway. The high possibility of endometrial carcinoma in postmenopausal women warrants that any patient who is symptomatic with PMB should be presumed to have endometrial cancer until the diagnostic evaluation process proves she does not.

CONTINUED ON PAGE 38

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The author reports being a consultant to Karl Storz Endoscopy and UVision360 and having other current financial relationships with Minerva Surgical and Gynesonics.

IN THIS ARTICLE

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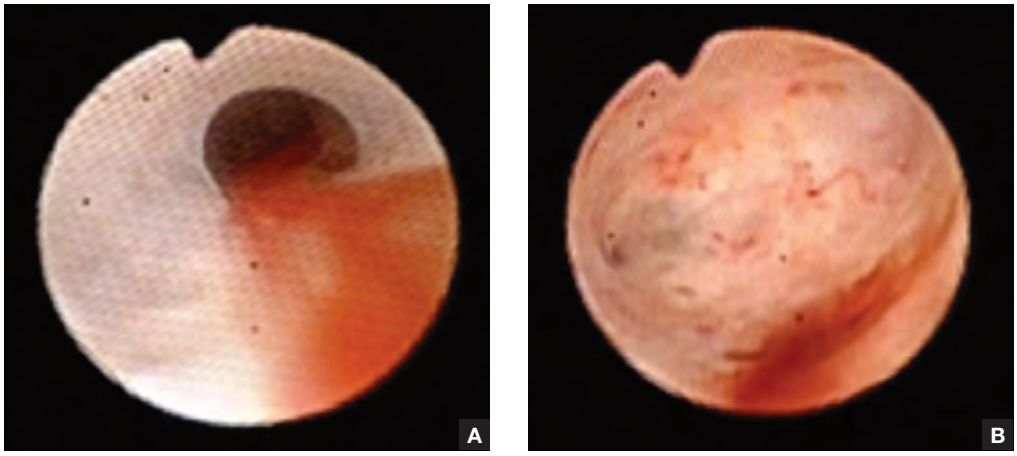
FIGURE 1 Endometrial atrophy



Flexible hysteroscope images (**A** and **B**) in a postmenopausal woman showing endometrial atrophy. Atrophy and endometrial breakdown are seen as subendometrial petechial hemorrhage and frank blood within the cavity. *Images courtesy of Amy Garcia.*

Evaluation of postmenopausal bleeding

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Endometrial biopsy is indicated when TVUS detects an endometrium >4 mm in a postmenopausal woman with AUB

Transvaginal ultrasound

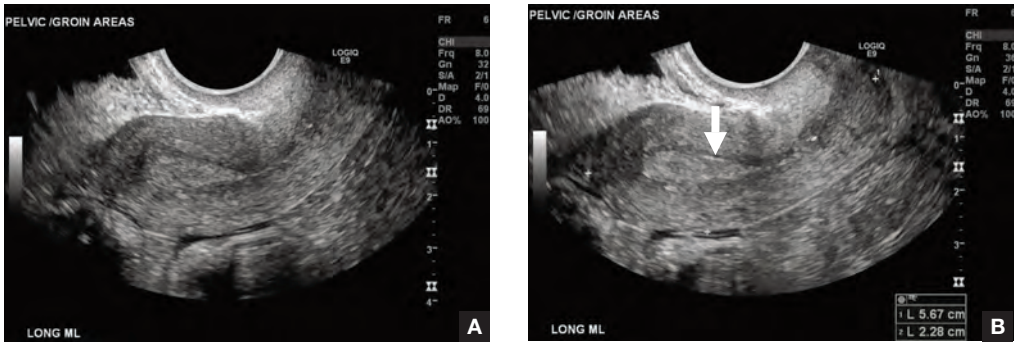
As mentioned, no general consensus exists for the evaluation of PMB; however, initial evaluation by TVUS is recommended. The American College of Obstetricians and Gynecologists (ACOG) concluded that when the endometrium measures ≤4 mm with TVUS, the likelihood that bleeding is secondary to endometrial carcinoma is less than 1% (negative predictive value 99%), and endometrial biopsy is not recommended.[3] Endometrial sampling in this clinical scenario likely will result in insufficient tissue for evaluation, and it is reasonable to consider initial management for atrophy. A thickened endometrium on TVUS (>4 mm in a postmenopausal woman with PMB) warrants additional evaluation with endometrial sampling (**FIGURE 2**).

Clinical takeaway. A thickened endometrium on TVUS ≥4 mm in a postmenopausal woman with PMB warrants additional evaluation with endometrial sampling.

Endometrial biopsy

An endometrial biopsy is performed to determine whether endometrial cancer or precancer is present in women with AUB. ACOG recommends that endometrial biopsy be

FIGURE 2 Anteverted uterus



(**A**) Transvaginal ultasound of an anteverted uterus in a symptomatic postmenopausal patient with postmenopausal bleeding showing a thickened endometrium. (**B**) The same image as A with an arrow (white) indicating the thickened endometrium. *Images courtesy of Amy Garcia.*

performed for women older than age 45. It is also appropriate in women younger than 45 years if they have risk factors for developing endometrial cancer, including unopposed estrogen exposure (obesity, ovulatory dysfunction), failed medical management of AUB, or persistence of AUB.[4]

Endometrial biopsy has some diagnostic shortcomings, however. In 2016 a systematic review and meta-analysis found that, in women with PMB, the specificity of endometrial biopsy was 98% to 100% (accurate diagnosis with a positive result). The sensitivity (ability to make an accurate diagnosis) of endometrial biopsy to identify endometrial pathology (carcinoma, atypical hyperplasia, and polyps) is lower than typically thought. These investigators found an endometrial biopsy failure rate of 11% (range, 1% to 53%) and rate of insufficient samples of 31% (range, 7% to 76%). In women with insufficient or failed samples, endometrial cancer or precancer was found in 7% (range, 0% to 18%).[5] Therefore, a negative tissue biopsy result in women with PMB is not considered to be an endpoint, and further evaluation with hysteroscopy to evaluate for focal disease is imperative. The results of endometrial biopsy are only an endpoint to the evaluation of PMB when atypical hyperplasia or endometrial cancer is identified.

Clinical takeaway. A negative tissue biopsy result in women with PMB is not considered to be an endpoint, and further evaluation with hysteroscopy to evaluate for focal disease is imperative.

Hysteroscopy

Hysteroscopy is the gold standard for evaluating the uterine cavity, diagnosing intrauterine pathology, and operative intervention for some causes of AUB. It also is easily performed in the office. This makes the hysteroscope an essential instrument for the gynecologist. Dr. Linda Bradley, a preeminent leader in hysteroscopic surgical education, has coined the phrase, "My hysteroscope is my stethoscope."[6] As gynecologists, we should be as adept at using a hysteroscope in the office as the cardiologist is at using a stethoscope.

FIGURE 3 Diagnostic hysteroscope

Side-by-side comparison of a small flexible diagnostic hysteroscope with a pipelle biopsy curette. Both are 3.0 mm in diameter. The small size and flexible nature of the hysteroscope facilitates evaluation of postmenopausal bleeding for a woman who may have a narrow or stenotic cervix. *Image courtesy of Amy Garcia.*

It has been known for some time that hysteroscopy improves our diagnostic capabilities over blinded procedures such as endometrial biopsy and dilation and curettage (D&C). As far back as 1989, Dr. Frank Loffer reported the increased sensitivity (ability to make an accurate diagnosis) of hysteroscopy with directed biopsy over blinded D&C (98% vs 65%) in the evaluation of AUB.[7] Evaluation of the endometrium with D&C is no longer recommended; yet today, few gynecologists perform hysteroscopic-directed biopsy for AUB evaluation instead of blinded tissue sampling despite the clinical superiority and in-office capabilities (**FIGURE 3**).

Hysteroscopy and endometrial carcinoma

The most common type of gynecologic cancer in the United States is endometrial adenocarcinoma (type 1 endometrial cancer). There is some concern about the effect of hysteroscopy on endometrial cancer prognosis and the spread of cells to the peritoneum at the time of hysteroscopy. A large meta-analysis found that hysteroscopy performed in the presence of type 1 endometrial cancer statistically significantly increased the likelihood of positive intraperitoneal cytology; however, it did not alter the

FAST TRACK

In postmenopausal women with AUB, negative endometrial biopsy results should be followed by hysteroscopic evaluation for focal disease

Three clinical scenarios

A common occurrence in the evaluation of postmenopausal bleeding (PMB) is an initial TVUS finding of an enlarged endometrium and an endometrial biopsy that is negative or reveals scant or insufficient tissue. Unfortunately, the diagnostic evaluation process often stops here, and a diagnosis for the PMB is never actually identified. Here are several clinical scenarios that highlight the need for hysteroscopy in the initial evaluation of PMB, especially when there is a discordance between transvaginal ultrasonography (TVUS) and endometrial biopsy findings.

Patient 1: Discordant TVUS and biopsy, with benign findings

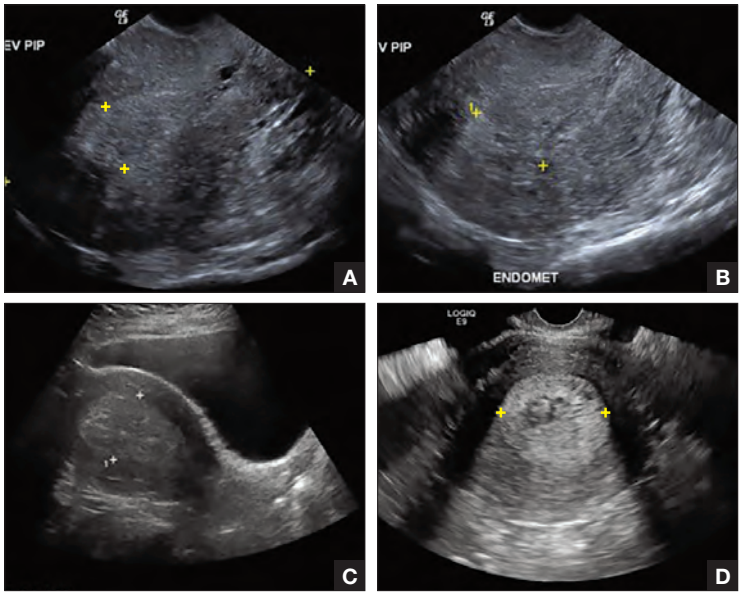
The patient is a 52-year-old woman who presented to her gynecologist reporting abnormal uterine bleeding (AUB). She has a history of breast cancer, and she completed tamoxifen treatment. Pelvic ultrasonography was performed; an enlarged endometrial stripe of 1.3 cm was found (**FIGURE 4A**). Endometrial biopsy was performed, showing adequate tissue but with a negative result. The patient is told that she is likely perimenopausal, which is the reason for her bleeding.

The following year, the patient has had continued AUB and is now postmenopausal by follicle-stimulating hormone level (FSH). TVUS is performed and the endometrium now measures 2.4 cm (**FIGURE 4B**). Subsequent endometrial biopsy shows scant tissue, and no additional evaluation is done. The following year, the patient still has PMB, and TVUS is performed. The endometrium now measures 4.7 cm (**FIGURES 4C, 4D**). The patient is taken to the operating room by the gynecologist for dilation and curettage (D&C). The results indicate scant, atrophic endometrium (hysteroscopy is not performed).

At the time of referral, the patient is evaluated with in-office hysteroscopy. Diagnosis of a 5 cm x 7 cm benign endometrial polyp is made. An uneventful hysteroscopic polypectomy is performed (**VIDEO 2**).

This scenario illustrates the shortcoming of initial evaluation by not performing a hysteroscopy, especially in a woman with a thickened endometrium with previous tamoxifen therapy. Subsequent visits failed to correlate bleeding etiology with discordant TVUS and endometrial biopsy results with hysteroscopy, and no hysteroscopy was performed in the operating room at the time of D&C.

FIGURE 4 TVUS evaluation of AUB



(**A**) Transvaginal ultrasound (TVUS) evaluation of abnormal uterine bleeding, with endometrial thickness of 1.3 cm in a patient with a history of tamoxifen therapy. (**B**) Image of second TVUS evaluation of postmenopausal bleeding (PMB), with endometrial thickness 2.4 cm. (**C**) Image of third TVUS evaluation of PMB, with endometrial thickness 4.7 cm. (**D**) Image of third TVUS evaluation of PMB, with endometrial thickness 4.7 cm.
Images courtesy of Amy Garcia.

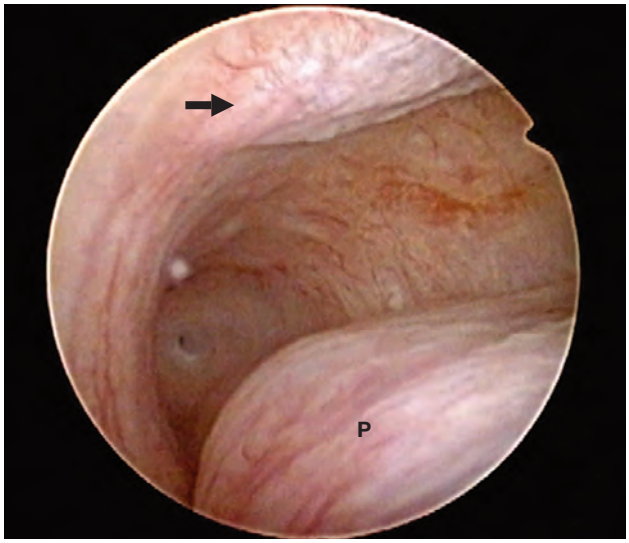
Patient 2: Discordant TVUS and biopsy, with premalignant findings

The patient is a 62-year-old woman who had incidental

clinical outcome. It was recommended that hysteroscopy not be avoided for this reason and is helpful in the diagnosis of endometrial cancer, especially in the early stages of disease.[8]

For endometrial cancer type 2 (serous carcinoma, clear cell carcinoma, and carcinosarcoma), Chen and colleagues reported a statistically significant increase in positive peritoneal cytology for cancers evaluated by hysteroscopy versus D&C. The disease-specific survival for the hysteroscopy group

FIGURE 5 Hysteroscopy, atypical hyperplasia



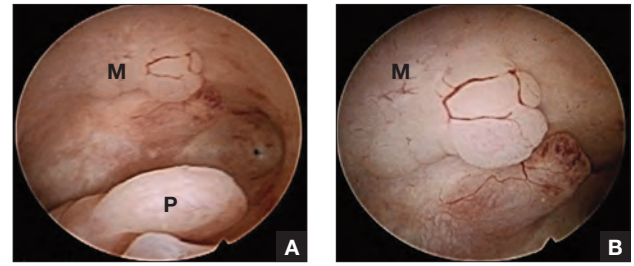
Hysteroscopic image of evaluation of postmenopausal bleeding with endometrial atrophy, benign polyp (P), and focal atypical hyperplasia (arrow). *Image courtesy of Amy Garcia*.

findings of a thickened endometrium on computed tomography scan of the pelvis. TVUS confirmed a thickened endometrium measuring 17 mm, and an endometrial biopsy showed scant tissue.

At the time of referral, a diagnostic hysteroscopy was performed in the office. Endometrial atrophy, a large benign appearing polyp, and focal abnormal appearing tissue were seen (**FIGURE 5**). A decision for polypectomy and directed biopsy was made. Histology findings confirmed benign polyp and atypical hyperplasia (**VIDEO 3**).

This scenario illustrates that while the patient was asymptomatic, there was discordance between the TVUS and endometrial biopsy. Hysteroscopy identified a benign endometrial polyp, which is common in asymptomatic postmenopausal patients with a thickened endometrium and endometrial biopsy showing scant

FIGURE 6 Hysteroscopy, adenocarcinoma



(**A**) Hysteroscopic image of endometrial atrophy with benign polyps (P) concomitant with adenocarcinoma (M) in a postmenopausal woman with bleeding. (**B**) Close-up of the adenocarcinoma (M) from image A. *Image courtesy of Amy Garcia*.

tissue. However, addition of the diagnostic hysteroscopy identified focal precancerous tissue, removed under directed biopsy.

Patient 3: Discordant TVUS and biopsy, with malignant findings

The patient is a 68-year-old woman with PMB. TVUS showed a thickened endometrium measuring 14 mm. An endometrial biopsy was negative, showing scant tissue. No additional diagnostic evaluation or management was offered.

At the time of referral, the patient was evaluated with in-office diagnostic hysteroscopy, and the patient was found to have endometrial atrophy, benign appearing polyps, and focal abnormal tissue (**FIGURE 6**). A decision for polypectomy and directed biopsy was made. Histology confirmed benign polyps and grade 1 adenocarcinoma (**VIDEOS 4A, 4B, 4C**).

This scenario illustrates the possibility of having multiple endometrial pathologies present at the time of discordant TVUS and endometrial biopsy. Hysteroscopy plays a critical role in additional evaluation and diagnosis of endometrial carcinoma with directed biopsy, especially in a symptomatic woman with PMB.

was 60 months, compared with 71 months for the D&C group. While this finding was not statistically significant, it was clinically relevant, and the effect of hysteroscopy on prognosis with type 2 endometrial cancer is unclear.[9]

Conclusion

Evaluation of PMB begins with a screening TVUS. Findings of an endometrium of ≤4 mm indicate a very low likelihood of the presence of endometrial cancer, and treatment for atrophy or changes to hormone

replacement therapy regimen is reasonable first-line management; endometrial biopsy is not recommended. For patients with persistent PMB or thickened endometrium ≥4 mm on TVUS, biopsy sampling of the endometrium should be performed. If the endometrial biopsy does not explain the etiology of the PMB with atypical hyperplasia or endometrial cancer, then hysteroscopy should be performed to evaluate for focal endometrial disease and possible directed biopsy. ●

References

1. ACOG Committee Opinion no. 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstet Gynecol*. 2018;131:e124-e129.
2. Goldstein SR. Appropriate evaluation of postmenopausal bleeding. *Menopause*. 2018;25:1476-1478.
3. Bel S, Billard C, Godet J, et al. Risk of malignancy on suspicion of polyps in menopausal women. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:138-142.
4. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol*. 2012;120:197-206.
5. van Hanegem N, Prins MM, Bongers MY. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:147-155.
6. Embracing hysteroscopy. September 6, 2017. https://consultqd.clevelandclinic.org/embracing-hysteroscopy/. Accessed July 22, 2019.
7. Loffer FD. Hysteroscopy with selective endometrial sampling compared with D&C for abnormal uterine bleeding: the value of a negative hysteroscopic view. *Obstet Gynecol*. 1989;73:16-20.
8. Chang YN, Zhang Y, Wang LP, et al. Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. *Fertil Steril*. 2011;96:957-961.
9. Chen J, Clark LH, Kong WM, et al. Does hysteroscopy worsen prognosis in women with type II endometrial carcinoma? *PLoS One*. 2017;12:e0174226.

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Video 1. Endometrial atrophy
Hysteroscopic evaluation of postmenopausal bleeding, with a 3-mm fiberoptic flexible hysteroscope.

Video 2. Large benign endometrial polyp
Flexible diagnostic hysteroscopy showing the tip of a large benign endometrial polyp and atrophic endometrium. The uterine cavity is difficult to distend secondary to the large polyp, which was removed hysteroscopically.

Video 3. Benign polyp, endometrial atrophy, and atypical hyperplasia
Hysteroscopic polypectomy of a large, benign polyp in a patient who also has endometrial atrophy and focal atypical hyperplasia. A small 5Fr hand-powered tissue removal device is used to remove the large polyp and atypical hyperplasia.

Video 4A. Hysteroscopic-directed biopsy of adenocarcinoma
Hysteroscopic-directed biopsy of focal abnormal tissue later confirmed as grade 1 adenocarcinoma.

Video 4B. Hysteroscopic polypectomy of small polyp
Hysteroscopic polypectomy of a small anterior polyp in a patient with multiple polyps and adenocarcinoma.

Video 4C. Hysteroscopic polypectomy of posterior benign polyp
Hysteroscopic polypectomy of a large posterior benign polyp in a patient with multiple polyps and adenocarcinoma.

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Expert advice for immediate postpartum LARC insertion

In this article: Who is the ideal patient for postpartum LARC; insertion technique, including avoiding common pitfalls; and tips for implementing immediate postpartum LARC within one's own institution

Q&A with Lisa Hofler, MD, MPH, MBA

IN THIS ARTICLE

Evidence-based education about long-acting reversible contraception (LARC) for women in the postpartum period can result in the increased continuation of and satisfaction with LARC.[1] However, nearly 40% of women do not attend a postpartum visit.[2] And up to 57% of women report having unprotected intercourse before the 6-week postpartum visit, which increases the risk of unplanned pregnancy.[3] The American College of Obstetricians and Gynecologists supports immediate postpartum LARC insertion as best practice,[3] and clinicians providing care for women during the peripartum period can counsel women regarding informed contraceptive decisions and provide guidance regarding both short-acting contraception and LARC.[1]

Immediate postpartum LARC, using intrauterine devices (IUDs) in particular, has been used around the world for a long time, says Lisa Hofler, MD, MPH, MBA, Chief in the Division of Family Planning at the University of New Mexico School of Medicine in Albuquerque. "Much of our initial data came from other countries, but eventually people in the United States said, 'This is a great option, why aren't we doing this?'" In addition, although women considering immediate postpartum LARC should be counseled about the theoretical risk of reduced duration of breastfeeding, the evidence overwhelmingly has not shown a negative effect on actual breastfeeding outcomes according to ACOG.[3] OBG MANAGEMENT recently met up with Dr. Hofler to ask her which patients are ideal for postpartum LARC, how to troubleshoot common pitfalls, and how to implement the practice within one's own institution.

Dr. Hofler is Chief, Division of Family Planning, Department of Obstetrics and Gynecology at the University of New Mexico School of Medicine in Albuquerque.

The author reports no financial relationships relevant to this article.

OBG MANAGEMENT: Who do you consider to be the ideal patient for immediate postpartum LARC?

Lisa Hofler, MD, MPH, MBA: The great thing about immediate postpartum LARC (including IUDs and implants) is that any woman is an ideal candidate. We are simply talking about the timing of when a woman chooses to get an IUD or an implant after the birth of her child. There is no one perfect woman; it is the person who chooses the method and wants to use that method immediately after birth. When a woman chooses a LARC, she can be assured that after the birth of her child she will be protected against pregnancy. If she chooses an IUD as her LARC method, she will be comfortable at insertion because the cervix is already dilated when it is inserted.

TABLE US Medical Eligibility Criteria classification of immediate postpartum LARC[3]

US MEC category	Description
Intrauterine device	
1 (A condition for which there is no restriction for the use of the contraceptive method)	Immediate postpartum IUD insertion
2 (A condition for which the advantages of using the method generally outweigh the theoretical or proven risks)	Immediate postpartum levonorgestrel (LNG)-IUD insertion in breastfeeding women
2	Copper or LNG-IUD insertion from 10 minutes after placental delivery to 4 weeks postpartum
1	Copper or LNG-IUD insertion at or after 4 weeks postpartum
4 (A condition that represents an unacceptable health risk if the contraceptive method is used)	Uterine infection or ongoing postpartum hemorrhage
Implant	
1	Insertion in nonbreastfeeding women less than 21 days postpartum
2	Insertion in breastfeeding women less than 30 days postpartum
1	Insertion in breastfeeding women beyond 30 days postpartum

For the implant, the contraindications are the same as in the outpatient setting. The Centers for Disease Control and Prevention's Medical Eligibility Criteria for Contraceptive Use covers many medical conditions and whether or not a person might be a candidate for different birth control methods.[4] Those same considerations apply for the implant postpartum (**TABLE**).[3]

For the IUD, similarly, anyone who would not be a candidate for the IUD in the outpatient setting is not a candidate for immediate postpartum IUD. For instance, if the person has an intrauterine infection, you should not place an IUD. Also, if a patient is hemorrhaging and you are managing the hemorrhage (say she has retained placenta or membranes or she has uterine atony), you are not going to put an IUD in, as you need to attend to her bleeding.

OBG MANAGEMENT: What is your approach to counseling a patient for immediate postpartum LARC?

Dr. Hofler: The ideal time to counsel about postbirth contraception is in the prenatal period, when the patient is making decisions about what method she wants to use after the birth. Once she chooses her preferred method, address timing if appropriate. It is less ideal to talk to a woman about the option of immediate postpartum LARC when she comes to labor and delivery, especially if that is the first time she has heard about it. Certainly, the time to talk about postpartum LARC options is not immediately after the baby is born. Approaching your patient with, "What do you want for birth control? Do you want this IUD? I can put it in right now," can feel coercive. This approach does not put the woman in a position in which she has enough decision-making time or time to ask questions.

OBG MANAGEMENT: What problems do clinicians run into when placing an immediate postpartum IUD, and can you offer solutions?

Dr. Hofler: When placing an immediate postpartum IUD, people might run into a few problems. The first relates to preplacement counseling. Perhaps when making the plan for the postpartum IUD the clinician did not counsel the woman that there are certain conditions that could preclude IUD placement—such as intrauterine infection or postpartum

FAST TRACK

Counsel patients prenatally about the contraindications to immediate postpartum IUD placement (intrauterine infection and postpartum hemorrhage) and make a back-up plan

Levonorgestrel vs copper IUD expulsion rates after immediate postpartum insertion

A 2017 prospective cohort study was the first to directly compare expulsion rates of the levonorgestrel (LNG) intrauterine device (IUD) and the copper IUD placed postplacentally (within 10 minutes of placental delivery). The study investigators found that, among 96 women at 12 weeks, 38% of the LNG-IUD users and 20% of the copper IUD users experienced IUD expulsion (odds ratio, 2.55; 95% confidence interval [CI], 0.99–6.55; *P* = .05). Women were aged 18 to 40 and had a singleton vaginal delivery at ≥35 weeks' gestation.[1] The two study groups were similar except that more copper IUD users were Hispanic (66% vs 38%) and fewer were primiparous (16% vs 31%). The study authors found the only independent predictor of device expulsion to be IUD type.

In a 2019 prospective cohort study, Hinz and colleagues compared the 6-month expulsion rate of IUDs inserted in the immediate postpartum period (within 10 to 15 minutes of placental delivery) after vaginal or cesarean delivery.[2] Women were aged 18 to 45 years and selected a LNG 52-mg IUD (75 women) or copper IUD (58 women) for postpartum contraception. They completed a survey from weeks 0 to 5 and on weeks 12 and 24 postpartum regarding IUD expulsion, IUD removal, vaginal bleeding, and breastfeeding. A total of 58 women had a vaginal delivery, and 56 had a cesarean delivery.

At 6 months, the expulsion rates were similar in the two groups: 26.7% of the LNG-IUDs expelled, compared with 20.5% of the copper IUDs (*P* = .38). The study groups were similar, point out the study investigators, except that the copper IUD users had a higher median parity (3 vs 2; *P* = .03). In addition, the copper IUDs were inserted by more senior than junior residents (46.2% vs 22.7%, *P* = .02).

A 2018 systematic review pooled absolute rates of IUD expulsion and estimated adjusted relative risk (RR) for IUD type. A total of 48 studies (rated from poor to good quality) were included in the analysis, and results indicated that the LNG-IUD was associated with a higher risk of expulsion at less than 4 weeks postpartum than the copper IUD (adjusted RR, 1.91; 95% CI, 1.50–2.43).[3]

References

1. Goldthwaite LM, Sheeder J, Hyer J, et al. Postplacental intrauterine device expulsion by 12 weeks: a prospective cohort study. *Am J Obstet Gynecol*. 2017;217:674.e1-674.e8.
2. Hinz EK, Murthy A, Wang B, et al. A prospective cohort study comparing expulsion after postplacental insertion: the levonorgestrel versus the copper intrauterine device. *Contraception*. May 17, 2019. doi: 10.1016/j.contraception.2019.04.011.
3. Jatlaoui TC, Whiteman MK, Jeng G, et al. Intrauterine device expulsion after postpartum placement. *Obstet Gynecol*. 2018:895-905.

hemorrhage. When dealing with those types of issues, a patient is not eligible for an IUD, and she should be mentally prepared for this type of situation. Let her know during the counseling before the birth that immediately postpartum is a great time and opportunity for effective contraception placement. Tell her that hopefully IUD placement will be possible but that occasionally it is not, and make a back-up plan in case the IUD cannot be placed immediately postpartum.

The second unique area for counseling with immediate postpartum IUDs is a slightly increased risk of expulsion of an IUD placed immediately postpartum compared with in the office. The risk of expulsion varies by type of delivery. For instance, cesarean delivery births have a lower expulsion rate than vaginal births. The expulsion rate seems to vary by type of IUD as well. Copper IUDs seem to have a slightly lower expulsion rate than hormonal IUDs. (See "Levonorgestrel vs copper IUD expulsion rates after immediate postpartum insertion.") This consideration should be talked about ahead of time, too. Provider training in IUD placement does impact the likelihood of expulsion, and if you place the IUD at the fundus, it is less likely to expel. (See "Inserting the immediate postpartum IUD after vaginal and cesarean birth step by step.")

A third issue that clinicians run into is actually the systems of care—making sure that the IUD or implant is available when you need it, making sure that documentation happens the way it should, and ensuring that the follow-up billing and revenue cycle happens so that the woman gets the device that she wants and the providers get paid for having provided it. These issues require a multidisciplinary team to work through in order to ensure that postpartum LARC placement is a sustainable process in the long run.

Often, when people think of immediate

postpartum LARC they think of postplacental IUDs. However, an implant also is an option, and that too is immediate postpartum LARC. Placing an implant is often a lot easier to do after the birth than placing an IUD. As clinicians work toward bringing an immediate postpartum LARC program to their hospital system, starting with implants is a smart thing to do because clinicians do not have to learn or teach new clinical skills. Because of that, immediate postpartum implants are a good troubleshooting mechanism for opening up the conversation about immediate postpartum LARC at your institution.

OBG MANAGEMENT: What advice do you have for administrators or physicians looking to implement an immediate postpartum LARC program into a hospital setting?

Dr. Hofler: Probably the best single resource is the American College of Obstetricians and Gynecologists' Postpartum Contraception Access Initiative (PCAI). They have a

Inserting the immediate postpartum IUD after vaginal or cesarean birth step by step

Technique for placing an IUD immediately after vaginal birth

1. Bring supplies for intrauterine device (IUD) insertion: the IUD, posterior blade of a speculum or retractor for posterior vagina, ring forceps, curved Kelly placenta forceps, and scissors.
2. Determine that the patient still wants the IUD and is still medically eligible for the IUD. Place the IUD as soon as possible following placenta delivery; in most studies IUD placement occurred within 10 minutes of the placenta. Any perineal lacerations should be repaired after IUD placement.
3. Break down the bed to facilitate placement. If the perineum or vagina is soiled with stool or meconium then consider povodine-iodine prep.
4. Place the posterior blade of the speculum into the vagina and grasp the anterior cervix with the ring forceps.
5. Set up the IUD for insertion: Change into new sterile gloves. Remove the IUD from the inserter. For levonorgestrel IUDs, cut the strings so that the length of the IUD and strings together is approximately 10 to 12 cm; copper IUDs do not need strings trimmed. Hold one arm of the IUD with the long Kelly placenta forceps so that the stem of the IUD is approximately parallel to the shaft of the forceps.
6. Insert the IUD: Guide the IUD into the lower uterine segment with the left hand on the cervix ring forceps and the right hand on the IUD forceps. After passing the IUD through the cervix, move the left hand to the abdomen and press the fundus posterior and caudad to straighten the endometrial canal and to feel the IUD at the fundus. With the right hand, guide the IUD to the fundus; this often entails dropping the hand significantly and guiding the IUD much more anteriorly than first expected.
7. Release the IUD with forceps wide open, sweeping the forceps to one side to avoid pulling the IUD out with the forceps.
8. Consider use of ultrasound guidance and ultrasound verification of fundal location, especially when first performing postplacental IUD placements.

Troubleshooting tips:

- If you are unable to visualize the anterior cervix, try to place the ring forceps by palpation.
- If you are unable to grasp the cervix with ring forceps by palpation, you may try to place the IUD manually. Hold the IUD between the first and second fingers of the right hand and place the IUD at the fundus. Release the IUD with the fingers wide open and remove the hand without removing the IUD.

Technique for placing an IUD immediately after cesarean birth

1. Determine that the patient still wants the IUD and is still medically eligible for the IUD. Place the IUD as soon as possible following placenta delivery; in most studies IUD placement occurred within 10 minutes of the placenta.
2. For levonorgestrel IUDs: Remove the IUD from the inserter. Cut the strings so that the length of the IUD and strings together is approximately 10 to 12 cm. Place the IUD at the fundus with a ring forceps and tuck the strings toward the cervix. It is not necessary to open the cervix or to place the strings through the cervix.
3. For copper IUDs: String trimming is not necessary. Place the IUD at the fundus with the IUD inserter or a ring forceps and tuck the strings toward the cervix. It is not necessary to open the cervix or to place the strings through the cervix.
4. Repair the hysterotomy as usual.

dedicated website (https://pcainitiative.acog.org/) and offer a lot of support and resources that include site-specific training at the hospital or the institution; clinician training on implants and IUDs; and administrator training on some of the systems of care, the billing process, the stocking process, and pharmacy education. They also provide information on all the things that should be included beyond the clinical aspects. I strongly recommend looking at what they offer.

Also, because many hospitals say, "We love this idea. We would support immediate postpartum LARC, we just want to make sure we get paid," the ACOG LARC Program website (https://www.acog.org/About-ACOG/ACOG-Departments/Long-Acting-Reversible-Contraception/Immediate-Postpartum-LARC-Medicaid-Reimbursement) includes state-specific guidance for how Medicaid pays for LARC devices. There is state-specific guidance about how the device payment can be separated from the global payment for delivery—specific things for each institution to do to get reimbursed. ●

References

1. Dole DM, Martin J. What nurses need to know about immediate postpartum initiation of long-acting reversible contraception. *Nurs Womens Health*. 2017;21:186-195.
2. American College of Obstetricians and Gynecologists. ACOG Committee Opinion no. 736: optimizing postpartum care. *Obstet Gynecol*. 2018;131:e140-e150.
3. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology, Long-Acting Reversible Contraception Work Group. Practice Bulletin no. 186: long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol*. 2017;130:e251-e269.
4. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep*. 2016;65:1-104.

Hormone therapy and cognition: What is best for the midlife brain?

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associated symptoms and cognitive performance: Results From the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2010;171:1214-1224.

16. Epperson CN, Sammel MD, Freeman EW. Menopause effects on verbal memory: findings from a longitudinal community cohort. *J Clin Endocrinol Metab*. 2013;98:3829-3838.
17. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology*. 1992;17:485-495.
18. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*. 2007;69:1074-1083.
19. Maki PM, Drogos LL, Rubin LH, et al. Objective hot flashes are negatively related to verbal memory performance in midlife women. *Menopause*. 2008;15:848-856.
20. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat Rev Neurol*. 2018;14:653-666.
21. de Villiers TJ, Hall JE, Pinkerton JV, et al. Revised global consensus statement on menopausal hormone therapy. *Climacteric*. 2016;19:313-315.
22. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10:819-828.
23. Drinking patterns and their definitions. Alcohol Research: Current Reviews website. January 2018. https://www.arcr.niaaa.nih.gov/arcr391/article02.htm. Accessed July 15, 2019.
24. Dixit AR, Crum RM. Prospective study of depression and the risk of heavy alcohol use in women. *Am J Psychiatry*. 2000;157:751-758.
25. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med*. 2010;8:348-353.
26. Bromberger JT, Kravitz HM, Chang YF, et al. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med*. 2011;41:1879-1888.
27. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *J Womens Health (Larchmt)*. 2019;28:117-134.

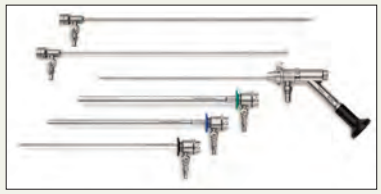
PRODUCT Update

OSPHENA HAS NEW INDICATION

Duchesnay Inc. has added moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy (VVA), due to menopause, to the indication of **Osphena**™ (ospemifene). The US Food and Drug Administration (FDA) approved **Duchesnay**'s supplemental New Drug Application in early 2019. Prior to this approval, **Osphena** was indicated only for the treatment of moderate to severe dyspareunia (painful intercourse), also a symptom of VVA, due to menopause. Osphena is nonhormonal and helps to improve vaginal tissues by increasing superficial cells, decreasing parabasal cells, and reducing vaginal pH, according to **Duchesnay**. The prescribing information for **Osphena** includes a boxed warning regarding endometrial cancer and cardiovascular disorders. Duchesnay encourages the reporting of negative adverse effects of prescription drugs to the FDA (www.fda.gov/medwatch).

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

NEW 3-IN-1 HYSTEROSCOPE



Hologic has a new 3-in-1 hysteroscope (**Omni**™), which became available for use in the United States in late 2018 after 510(k) clearance by the FDA. The device features a flexible, modular design offering powerful visualization with 3 sheath options to see and treat pathology, says **Hologic**. No longer will a physician be required to use a diagnostic scope to look in the uterine cavity for fibroids or polyps, and then switch to an operative scope to biopsy or treat the pathology. **Omni**'s sheaths also are designed with smaller diameters (3.7 mm diagnostic sheath; 5 mm operative sheath; 6 mm operative sheath) to reduce required dilation, promoting patient comfort. In addition, the device features a long (200 mm) working length to facilitate access and treatment in obese patients, according to the manufacturer. Consult the device's instructions for use benefit and risk information.

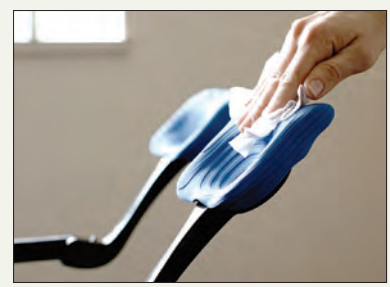
FOR MORE INFORMATION, VISIT: https://gynsurgicalsolutions.com/product/omni-hysteroscope/.

SURGICAL RF TECHNOLOGY

FDA-cleared **TempSure**™ Surgical RF Technology is now available in North America, **Hologic**'s Cynosure division announced. The **TempSure** radiofrequency platform provides clinicians with the ability to perform both surgical and nonsurgical aesthetic procedures across a variety of specialties, on a single device, says **Hologic**. Cynosure also has returned **TempSure**™ **Vitalia** hand pieces and probes to the market and will continue to market its **MonaLisa Touch**™ CO2 laser following the FDA's inquiry on products used in energy-based women's health procedures. Cynosure says that it has worked closely with the FDA and reviewed and updated all of its marketing and promotional materials to ensure that they are consistent with the FDA's labeling expectations.

FOR MORE INFORMATION, VISIT:
https://www.cynosure.com/tempsure-platform.

PROFESSIONAL FOOT SUPPORTS



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Which birth defects are associated with childhood[a] cancer risk?

Children with **chromosomal birth defects** are **11.6 times** more likely than children born without birth defects to be diagnosed with cancer

Trisomy 21	Acute lymphoblastic leukemia, acute myeloid leukemia
Trisomy 18	Hepatoblastoma
Neurofibromatosis	Astrocytoma, non-rhabdomyosarcoma soft tissue sarcomas

Children with **nonchromosomal birth defects** are **2.5 times** more likely than children born without birth defects to be diagnosed with cancer

Congenital anomalies of the nervous system	Non-rhabdomyosarcoma soft tissue sarcomas, astrocytoma, ependymoma, epithelial neoplasms
Congenital anomalies of the heart and circulatory system	Neuroblastoma, hepatoblastoma
Congenital anomalies of the digestive system	Medulloblastoma, non-Hodgkin lymphoma
Congenital anomalies of the genitourinary system	Wilms tumor, extracranial germ cell tumors, hepatoblastoma, neuroblastoma, non-rhabdomyosarcoma soft tissue sarcomas
Congenital anomalies of the musculoskeletal system	Extracranial germ cell tumors, hepatoblastoma

Children with **4 or more major birth defects** are **5.9 times** more likely than children born without birth defects to be diagnosed with cancer

[a]Children were followed up to age 18. The source study pooled data from 4 state cancer registries on 10,181,074 children born from January 1, 1992 to December 31, 2013.

Source: Lupo PJ, Schraw JM, Desrosiers, TA, et al. Association between birth defects and cancer risk among children and adolescents in a population-based assessment of 10 million live births. *JAMA Oncol*. Published online June 20, 2019. doi:10.1001/jamaoncol.2019.1215

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OBG MANAGEMENT

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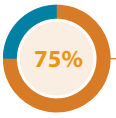
The value of care:

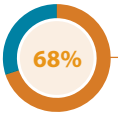
UNIVERSAL SCREENING
for Chlamydia and Gonorrhea

About **ONE** in **TWO** sexually active people will acquire an STI by **AGE 25.**

Infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are commonly asymptomatic.



~75% of women infected with **chlamydia** are asymptomatic[1]



~68% of women infected with **gonorrhea** are asymptomatic[1]

Chlamydia and gonorrhea are two of the most common reportable sexually transmitted infections (STIs) and rates of infection are on the rise.

A universal screening CT/NG strategy would focus on women within the high-risk age group covered by guidelines from USPSTF and CDC guidelines (women 15-24 years old) without regard to the sexual activity they report.

Universal screening may help to:[2]

- Decrease STI prevalence
- Decrease infertility due to undiagnosed infections
- Reduce health care cost

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References
1. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. *Prev Med.* 2003;36(4)502-509.
2. Owusu-Edusei K, Hoover KW, Gift TL. Cost-effectiveness of opt-out chlamydia testing for high-risk young women in the U.S. *Am J Prev Med.* 2016;51(2):216-24. doi: 10.1016/j.amepre.2016.01.007.