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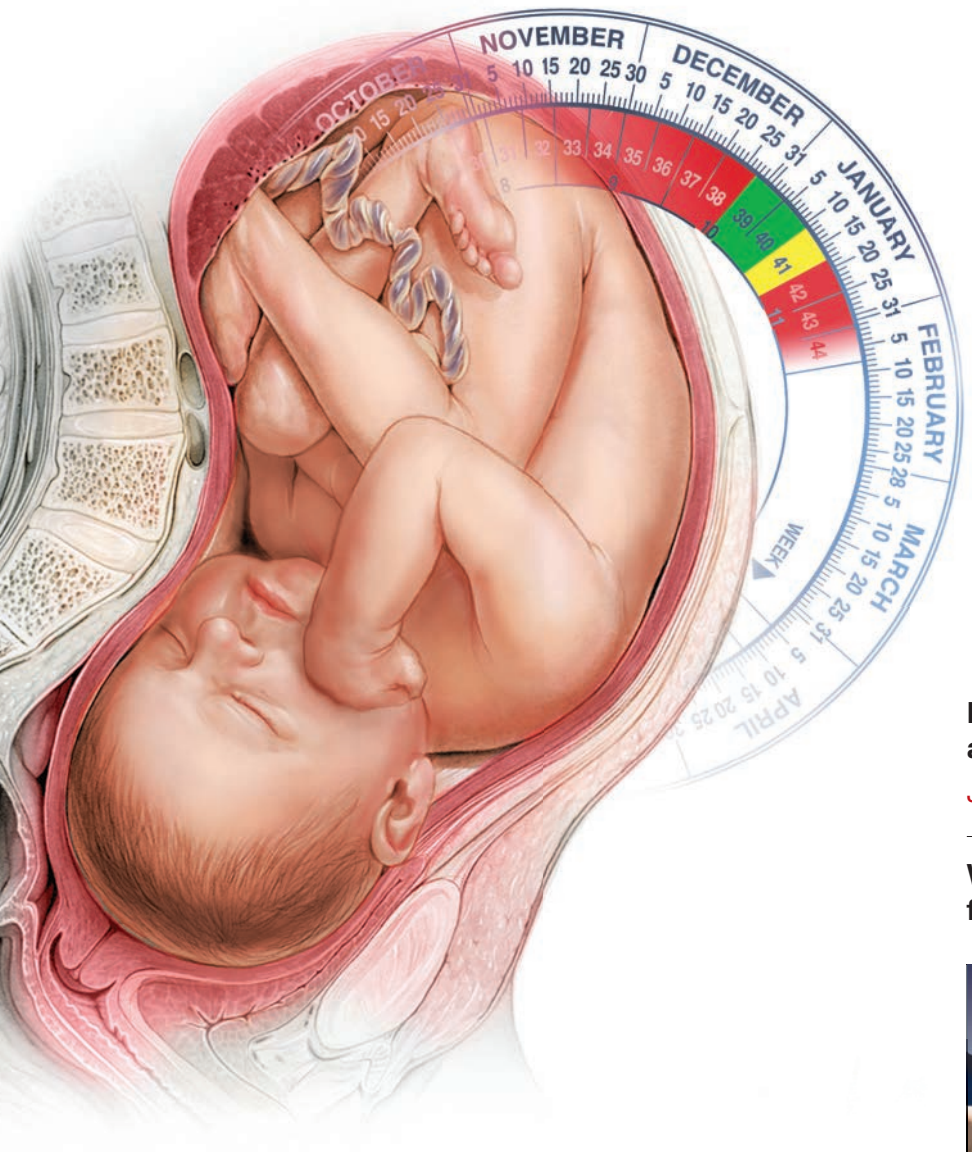
OBG MANAGEMENT



HPV vaccine for adults: Counseling implications
Barbara Levy, MD; Levi S. Downs Jr, MD

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IUDs for never-sexually-active teens: A good choice?

Does elective induction at 39 weeks benefit mom and baby?

Jaimey M. Pauli, MD

Managing menopausal symptoms after breast cancer
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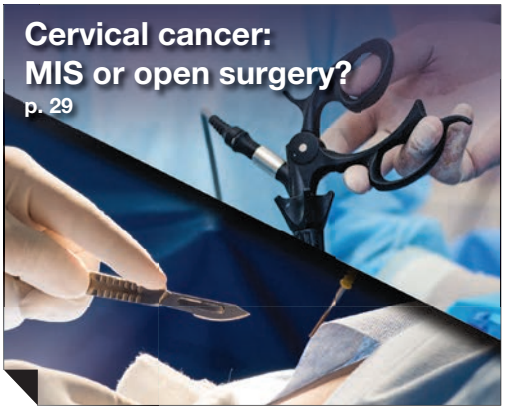
We can affect health care costs for patients



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

LARC = long-acting reversible contraceptive

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

WOMN-1267530-0000 09/18

NEXPLANON is the only non-uterine LARC option

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

Placed subdermally in the inner upper arm just under the skin

(Actual implant shown; actual implant is 4 cm)

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

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

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

1. **Complications of Insertion and Removal**

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

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

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

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

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

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

2. **Changes in Menstrual Bleeding Patterns**

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

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

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

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

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

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

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

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

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

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

3. **Ectopic Pregnancies**

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

4. **Thrombotic and Other Vascular Events**

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

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

5. **Ovarian Cysts**

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

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

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

7. **Liver Disease**

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

8. **Weight Gain**

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

9. **Elevated Blood Pressure**

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

10. **Gallbladder Disease**

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

11. **Carbohydrate and Lipid Metabolic Effects**

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

12. **Depressed Mood**

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

13. **Return to Ovulation**

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives

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

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

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

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

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

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

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

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

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

The value of care:
CANCER PREVENTION

From screening to diagnosis, treatment decisions, and surveillance, LabCorp supports the continuum of care. Our advanced technologies enable clinicians to detect and define the disease more accurately for informed treatment decisions, including hereditary breast and ovarian cancer testing (*BRCA 1* and *2*), VistaSeq® hereditary cancer panels, cervical cytology, colorectal and thyroid screening.

Value beyond testing. LabCorp's full-service offerings, specialty test options, genetic counseling programs, cost estimator, and coast-to-coast patient service centers set our value apart and put your patients at the heart of our efforts to improve health and improve lives.

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

LabCorp

JANUARY 2019 | VOL 31, NO 1

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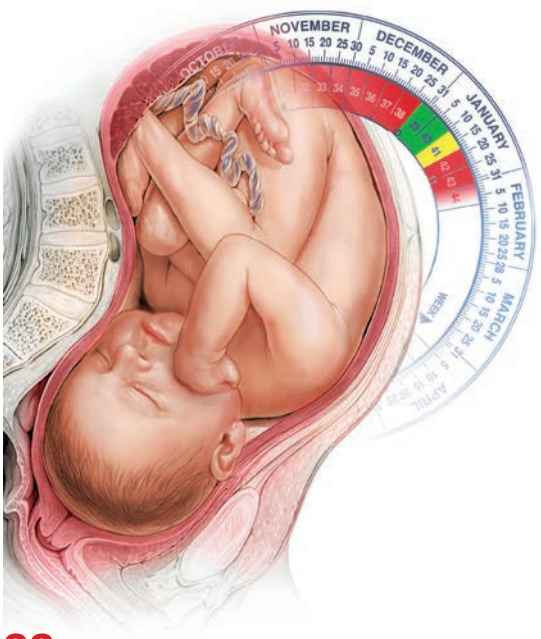

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*S. Maheux-Lacroix et al. Hum Reprod 2014;29(5):953-63.

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The HPV vaccine is now recommended for adults aged 27–45: Counseling implications

Can we improve human papillomavirus (HPV) vaccination rates among boys and girls so "catch-up" vaccinations in adults are unnecessary?

Barbara Levy, MD
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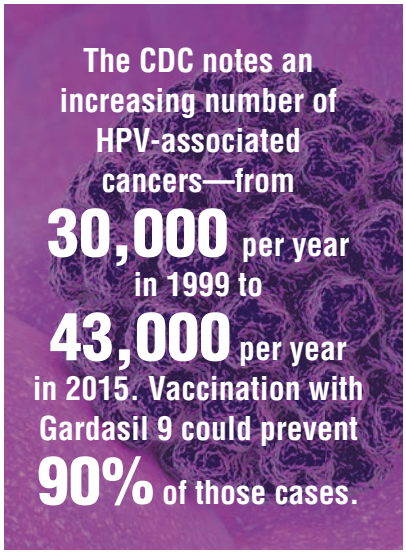
The US Food and Drug Administration (FDA) recently extended the approval for Gardasil 9 (to prevent HPV-associated cancers, cancer precursors, and genital lesions) to men and women aged 27 to 45.[1] In this editorial, we discuss the evolution of the HPV vaccine since its initial approval more than 10 years ago, the benefits of primary prevention with the HPV vaccine, and the case for the FDA's recent extension of coverage to older men and women.

The evolution of the HPV vaccine

Since recognition in the 1980s and 90s that high-risk strains of HPV, notably HPV types 16 and 18, were linked to cervical cancer, there have been exciting advances in detection and prevention of high-risk HPV infection. About 70% of cervical cancers are attributable to these 2 oncogenic types.[2] The first vaccine licensed, Gardasil (Merck), was approved in 2006 for girls and women aged 9 through 26 to prevent HPV-related diseases caused by types 6, 11, 16, and 18.[3] The vaccine was effective for prevention of cervical cancer; genital warts; and grades 2 and 3 of cervical, vulvar, and vaginal intraepithelial neoplasia. In 2008, prevention of vulvar and vaginal cancers was added to the indication. By 2009, prevention of genital warts was added, and use in males aged 9 to 15 was approved. By 2010 sufficient data were accumulated to document prevention of anal cancer and anal intraepithelial neoplasia in men and women, and this indication was added.

In 2014 Gardasil 9 was approved to extend coverage to an additional 5 oncogenic HPV types (31, 33, 45, 52, and 58), now covering an additional 20% of cervical cancers, and in 2015 Gardasil 9 indications were expanded to include boys and men 9 to 26 years of age. Immunogenicity studies were performed to infer effectiveness of a 2-dose regimen in boys and girls aged 9 to 14 years, which was recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in late 2016.[4]

Until October 2018, Gardasil 9 was indicated for prevention of genital warts, cervical, vaginal, vulvar and anal cancers and cancer precursors for males and females aged 9 to 26 years. In October the FDA extended approval of the 3-dose vaccine regimen to men and women up to age 45.



HPV vaccine uptake

HPV vaccination has been underutilized in the United States. In 2017, a disappointing 49% of adolescents were up to date on vaccination, and 66% had received at least one dose.[5] In rural areas the vaccination rates are 11 points lower than in urban regions.[6] The CDC notes an increasing

The authors report no financial disclosures related to this article.

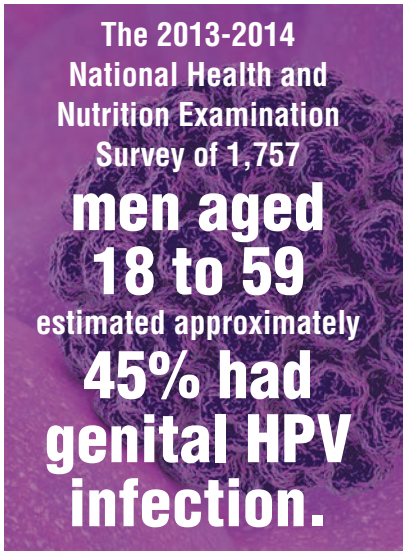
number of HPV-associated cancers—from 30,000 per year in 1999 to 43,000 per year in 2015—due mostly to increases in oral and anal carcinomas. Vaccination with Gardasil 9 could prevent 90% of those cases.[7]

Non-US successes. HPV vaccine uptake in Australia provides an excellent opportunity to study the impact of universally available, school-based vaccinations. In 2007 Australia implemented a program of free HPV vaccination distributed through schools. Boys and girls aged 12 and 13 were targeted that year, with catch-up vaccinations for those aged 13 to 18 in 2007-2009 in schools and for those aged 18 to 26 reached in the community.[8]

Ali and colleagues studied the preprogram and postprogram incidence of genital warts.[9] About 83% received at least 1 dose of vaccine, and 73% of the eligible population completed the 3-dose regimen. There was a significant reduction in warts in both men and women younger than age 21 from 2007 to 2011 (12.1% to 2.2% in men and 11.5% to 0.85% in women). In the 21 to 30 age group there were similar reductions. This study demonstrates that with universal access and public implementation, the rates of HPV-associated disease can be reduced dramatically.

Data informing expanded vaccination ages

Will vaccination of an older population, with presumably many of whom sexually active and at risk for prior exposure to multiple HPV types, have a reasonable impact on lowering HPV-associated cancers? Are HPV-detected lesions in 27- to 45-year-old women the result of reactivation of latent HPV infection, or are they related to new-onset exposure? The FDA reviewed data from 3 studies of HPV vaccination in women aged 27 to 45. The first enrolled women who were naïve to oncogenic HPV types and provided all 3 doses of quadrivalent vaccine were followed for 4 years, along with a comparison group of nonvaccinated women. The second study allowed the nonvaccinated group to receive vaccine in year 4. Both groups were followed up to 10 years with the relevant outcome defined as cumulative incidence of HPV 6/11/16/18-related CIN and condyloma. The third study looked at the same outcomes in a set of all women—whether HPV high-risk naïve or not—after receiving vaccine and followed more than 10 years.[7] This last study is most relevant to ObGyns, as it is closest to how we would consider vaccinating our patients.



The study findings are reassuring: A large proportion of HPV infections in women between 27 and 45 are the result of new exposure/infection. A study of 420 online daters aged 25 to 65 showed an annual incidence of high-risk HPV types in vaginal swabs of 25.4%, of which 64% were likely new acquisitions.[10] The 2013-2014 National Health and Nutrition Examination Survey of 1,757 men aged 18 to 59 estimated approximately 45% had genital HPV infection. There was a bimodal distribution of disease with peaks at 28 to 32 and a larger second peak at 58 to 59 years of age.[11] Bottom line: Men and women older than age 26 who are sexually active likely acquire new HPV infections with oncogenic types. Exposure to high-risk HPV types prior to vaccination—as we would expect in the real-world setting—did not eliminate the substantial benefit of immunization.

Based on these study results, and extrapolation to the 9-valent vaccine, the FDA extended the approval of Gardasil 9 to men and women from age 9 to 45. The indications and usage will remain the same: for prevention of cervical, vulvar, vaginal, and anal cancer and genital warts as well as precancerous or dysplastic lesions of the cervix, vulva, vagina, and anus related to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Impact of the new indication on HPV-related disease

As described above, widespread vaccination of young girls and boys is going to have major impact on HPV-related disease, including precancer and cancer. Because there is evidence that older women and men are at risk for new HPV infection,[10] there likely will be some benefit from vaccination of adults. It is difficult, however, to extrapolate the degree to which adult vaccination will impact HPV-related disease. This is because we do not fully understand the rates at which new HPV infection in the cervices of older women will progress to high-grade dysplasia or cancer. Further, the pathophysiology of HPV-related cancers at other anogenital sites and new

oral-pharyngeal infection is poorly understood in comparison with our knowledge of the natural history of high-risk HPV infection in younger women. That said, because of the outstanding efficacy of HPV vaccination and the low-risk profile, even if the actual impact on prevention of cancer or morbidity from dysplasia is relatively low, adult vaccination benefits outweigh the limited risks.

It may be that increased vaccination and awareness of vaccination for adults may enhance the adherence and acceptance of widespread vaccination of boys and girls. Adult vaccination could create a cultural shift toward HPV vaccination acceptance when adult parents and loved ones of vaccine-age boys and girls have been vaccinated themselves.

Current and future insurance coverage

The Affordable Care Act, otherwise known as Obamacare, mandates coverage for all immunizations recommended by the ACIP. HPV vaccination up to age 26 is fully covered, without copay or deductible. The ACIP did consider extension of the indications for HPV vaccination to men and women up to age 45 at their October 2018 meeting. They are tasked with considering not only safety and efficacy but also the cost effectiveness of implementing vaccination. They continue to study the costs and potential benefits of extending HPV vaccination to age 45. Their recommendations may be determined at the February 2019 meeting—or even later in 2019. The American College of Obstetricians and Gynecologists (ACOG) relies upon ACIP for practice guidance. Once the ACIP has made a determination, and if new guidelines are published in the *Morbidity and Mortality Weekly Report*, insurance coverage and ACOG guidance will be updated.

How should we react and change practice based on this new indication?

Given the information reviewed by the FDA, ObGyns will want to discuss the availability of Gardasil 9 with our patients between ages 27 and 45 who have not been previously immunized. Especially for our patients with exposure to multiple or new sexual partners, immunization against oncogenic HPV viral types is effective in providing protection from cancer precursors and cancers of the cervix, vulva, vagina, and anus—and of course from genital warts. They should understand that, until formal recommendations are published by the ACIP, they are likely to be responsible for the cost of the vaccination series. These conversations will also remind our patients to immunize their teens against HPV. The more conversation we have regarding the benefits of vaccination against high-risk HPV types, the more likely we are to be able to achieve the impressive results seen in Australia. ●

Given the information reviewed by the FDA, ObGyns will want to discuss the availability of Gardasil 9 with **patients between ages 27 and 45** who have not been previously immunized.

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Is an IUD a good contraceptive choice for a never sexually active teen?

Yes, but some insertions may be required to be performed outside of the office setting.

Authors of this retrospective cohort study compared the success of attempted intrauterine device (IUD) insertion in women aged 10 to 20 years who were and were not sexually active. Insertion was successful on the first attempt in 90.2% and 96.1% of women in the never sexually active and sexually active groups, respectively (P = .086). Further, overall successful insertion rates in both groups were more than 98% when a second insertion attempt was performed. However, only 52.4% of the never sexually active women, compared with 94.5% of the sexually active women, had the IUD placed in an office setting (P<.001).

Kebodeaux CA, Schwartz BI. Experience with intrauterine device insertion in never sexually active adolescents: a retrospective cohort study. Am J Obstet Gynecol. 2018;219:600.e1-e7.

EXPERT COMMENTARY

Ronald T. Burkman, MD, is Emeritus Professor of Obstetrics and Gynecology, Tufts University School of Medicine, Baystate Medical Center, Springfield, Massachusetts.

Data demonstrate efficacy and safety of the IUD in adolescents. In addition, IUDs (particularly the levonorgestrel-containing IUD) have many noncontraceptive benefits. There is still reluctance, however, among clinicians to use IUDs in adolescents. In a sample of fellows of the American College of Obstetricians and Gynecologists, only 43% considered adolescents appropriate candidates for use of an IUD.[1]

The author reports no financial relationships relevant to this article.

Study details

In this retrospective chart review, Kebodeaux and Schwartz sought to compare successful IUD insertion rates on first attempt in 120 sexually active (SA) and 82 never sexually active (NSA) adolescents. The IUD type used for all women was the 52-mg levonorgestrel IUD (Mirena), except for 3 copper IUDs (Paragard) used in the SA group. The primary indications for IUD use were contraception (85.2%) in the SA group and abnormal uterine bleeding (43.9%) and menstrual suppression (24.4%) in the NSA group.

In the NSA group, 82.9% of adolescents had had some type of prior treatment affecting the menstrual cycle, compared with 60.9% in the SA group (P = .001).

Non–office insertion. Either a sedation unit or operating room was utilized in 5.5% of the

FAST TRACK

IUD insertion was successful on the first attempt in 90.2% of never sexually active adolescents and in 96.1% of sexually active teens

IUD insertions in the SA group and 47.6% of the NSA group. Among the 39 adolescents in the NSA group undergoing non–office insertion, 19 (48.7%) had special needs (learning or intellectual disabilities, autism/autism spectrum, or physical disabilities, such as cerebral palsy). Only 1 adolescent with special needs in the NSA group had an office insertion compared with 5 out of 6 in the SA group.

The performance of another procedure other than the IUD insertion (including diagnostic laparoscopy and hymenectomy) was common among adolescents undergoing procedures in the sedation unit or operating room who did not have special needs. It is also important to note that adolescents with special needs were routinely offered insertion under anesthesia while SA adolescents were offered insertion under anesthesia only if they were undergoing another procedure as well.

Study strengths and weaknesses

The study's strengths include IUD insertions performed at a children's hospital by providers with experience working with adolescent populations. This likely accounts for the high rates of "tolerance of the procedure well" (93.8% in the SA group vs 81.7% in the NSA group; $P = .006$). The study also included a patient population—adolescents with special needs—that has not been studied relative to IUD use previously.

A significant weakness of the study, however, is that there are no long-term follow-up data, particularly related to continuation rates. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

These study findings provide further support to combat the myth that adolescents, particularly if nulliparous or not sexually active, are not suitable candidates for IUD use. However, if they have never been sexually active or have special needs, IUD insertion under sedation or in an operating room may be necessary. It is also likely that selection of the IUD as an option by an adolescent and overall tolerance of the insertion procedure requires providers with experience in caring for adolescents as well as providers possessing good counseling skills.

RONALD T. BURKMAN, MD

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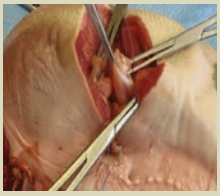

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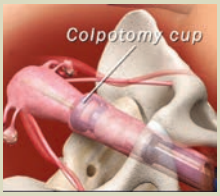

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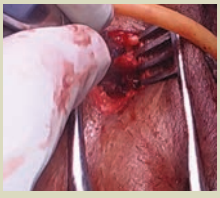

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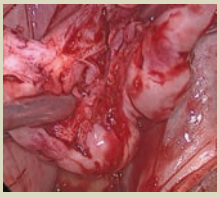

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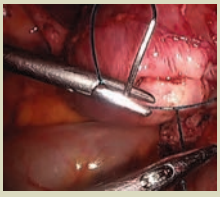

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Managing menopausal vasomotor and genitourinary symptoms after breast cancer

Two cases on selecting safe and useful treatments for survivors of breast cancer experiencing distressing quality-of-life symptoms of menopause

JoAnn V. Pinkerton, MD

IN THIS ARTICLE

Breast cancer survivors entering menopause face the risk of several menopausal symptoms:

Hot flashes, the most common symptom, occur in more than 75% of women during menopause and have the potential to persist for as long as 15 years.[1] That lengthy interval becomes a major issue for patients, especially when hot flashes are associated with other menopausal symptoms, including sleep disruption, difficulty concentrating, and emotional instability (crying, irritability).

- **Painful intercourse** and **loss of interest in sexual activity** often develop as a result of vaginal atrophy and dryness.
- **Urinary tract symptoms** include urgency and, compared to the patient's history, more frequent infections.
- **Bone loss** is a concern for many women after breast cancer, especially if they are, or have been, on aromatase inhibitor therapy.
- **Depression** might be related to hormonal changes due to menopause or hormonal therapies, a consequence of merely having a diagnosis of cancer, or an adverse effect of chemotherapy.

In this brief review, I'll examine options for treating symptoms of menopause by strategy—lifestyle modifications, over-the-counter treatments, and prescription drugs. Separately, I'll look at options for managing genitourinary syndrome of menopause (GSM).

Dr. Pinkerton is Professor, Department of Obstetrics and Gynecology, and Director, Midlife Health, University of Virginia Health System, Charlottesville, Virginia. She is also Executive Director of the North American Menopause Society. She serves on the OBG MANAGEMENT Board of Editors.

The author reports no financial relationships relevant to this article.

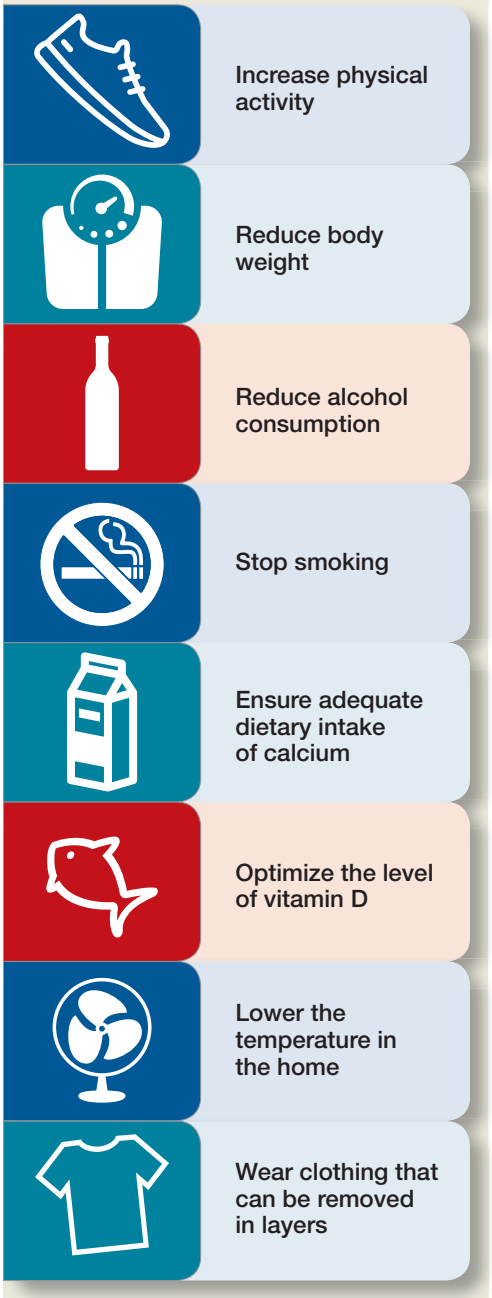
CASE 1

Rose is a 56-year-old woman who presents to clinic with a new breast mass, felt on breast self exam. The mass is about 1 cm, mobile, and firm. Diagnostic mammogram and ultrasound confirm a worrisome mass; biopsy returns positive with a 9-mm invasive, estrogen-receptor positive, ductal carcinoma with negative sentinel nodes at the time of lumpectomy. Radiation therapy was completed. She then met with oncology and decided against chemotherapy. Instead, she began an aromatase inhibitor 3 months ago. Bone density showed osteopenia. She presents to your office reporting frequent bothersome hot flashes and disrupted sleep.

Strategy #1: Lifestyle adaptations

First-line interventions for menopausal women who have had breast cancer usually involve taking a critical look at lifestyle and undertaking modifications that can alleviate discomfort. Because overall health is important for women who have had breast cancer,

Lifestyle strategies to managing vasomotor and genitourinary symptoms after breast cancer



you should, across the spectrum of patients, encourage them to:

- increase physical activity
- reduce body weight by approximately 10% (if overweight or obese)
- reduce alcohol consumption
- stop smoking
- ensure adequate intake of calcium (1,200 mg, preferably by diet)
- optimize the level of vitamin D, including by increasing intake of fresh fish, eggs, and numerous other fortified foods.

The value of nondrug therapy for hot flashes is difficult to prove. Certain lifestyle changes are sensible, even if not evidence-based, and will help some women (but not others). We suggest that patients try lowering the temperature in the home (65–68˚ at night); running a fan; wearing clothing that can be removed in layers; and avoiding triggers such as spicy food, alcohol, cigarettes, and hot drinks. Hypnosis and cognitive behavioral therapy (CBT) have been shown to help in clinical trials. Measures with benefit and minimal risks, but effectiveness not established, include acupuncture (sham worked as well as traditional), exercise, yoga, paced respiration, relaxation training, and mindfulness-based stress reduction.

Strategy #2: OTC compounds

Over-the-counter products—from soy products to black cohosh to flax seed, and including dong quai, evening primrose oil, maca, omegas, pollen extract, ginseng, and red clover,[2] or several compounds formulated in combination—have not been proven to be of more benefit for relieving symptoms of menopause than placebo in randomized trials, and thus might or might not be effective in a given patient. S-equol, a metabolite of a soy isoflavone taken by women who are non-equol producers, is available under the trade name Equelle and has shown some benefit. Note: There is concern that supplements that contain estrogen-like compounds, like soy products, might actually increase the risk of breast cancer. Dietary soy is not felt to be a concern.

Ask questions about the severity of a patient's hot flashes. When a patient reports hot flashes, and is requesting help to relieve her discomfort, inquire 1) how often she has hot flashes, 2) how severe they are, and 3) how bothered she is by them (not all women are equally troubled, of course). The patient's answers to these questions will help you decide

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Weigh hot flash frequency, severity, and the patient's reaction to them when considering an OTC treatment

Newly arrived and on the horizon

Where does this review of available treatments leave us? Regrettably, with many women who experience painful intercourse and vaginal dryness despite what is available for treating their problems, and who continue looking to medical science and women's health care for new options. So, what is coming next for these suffering patients? Here is a quick and selective run-through:

KNDy neurons. For hot flashes, there is the promise of nonhormonal treatment using these neurons, believed to be involved in reproduction by triggering expression of various compounds—particularly neurokinin B, which mediates hot flashes.[1]

Estetrol. In testing for use in treating hot flashes and its effect on GSM is this pregnancy-associated natural hormone that, importantly, did not stimulate breast cancer in a rat model.[2] More evidence of efficacy is needed.

Lasers. For vaginal atrophy, many women are choosing treatment with the laser. Keep in mind, however, that, although lasers are FDA-approved devices, they do not have the FDA's endorsement for use in vaginal atrophy, and have not been well-tested for their effectiveness for this indication in women with breast cancer who have taken an aromatase inhibitor. ACOG, NAMS, and the Endocrine Society have urged that additional trials be conducted, and have stated that the laser for vaginal atrophy cannot be recommended until there are more data on safety and efficacy.[2]

Lower-dose soft-gel vaginal estrogen suppositories have recently been approved by the FDA at 4 and 10 µg.[3] The formulations are only minimally absorbed, potentially making them a good option for women who have had breast cancer.

Lasofoxifene, a selective estrogen-receptor modulator not yet approved by the FDA, has been shown to ameliorate vaginal changes.[4] The drug is neutral or protective on the breast, but is now being tested in women with resistant breast cancer and unlikely to become available for GSM.

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which treatment option to offer, based on evidence and your experience.

CASE 1 Continued

Rose tried black cohosh OTC without improvement. She was interested in hypnosis but did not find it effective for her. She returned 3 months later stating that she is miserable, exhausted, not getting enough sleep, and her hot flashes and night sweats are affecting both her work and her relationship.

Strategy #3: Prescription medication

When addressing hot flashes, consider whether they occur more at night or during the day, or do not follow a day–night pattern. For women whose hot flashes occur mostly at night, and might therefore make sleeping difficult and cause fatigue and irritability, gabapentin, taken approximately 1 hour before bed, can be helpful. If tolerated without excessive somnolence the next day, the dose can be increased at night or additional doses provided during the day depending on hot flash response. For women who have hot flashes day and night, we often prescribe a low-dose antidepressant from the selective serotonin-reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) class.

When prescribing an antidepressant, we make a distinction between breast cancer patients who are taking tamoxifen and those who are not, to avoid cytochrome P450 2D6 inhibitors in women taking tamoxifen.[3] Better choices for women taking tamoxifen include desvenlafaxine, venlafaxine, escitalopram, or gabapentin or pregabalin.

For women with breast cancer who are taking an aromatase inhibitor, and who are also experiencing mood changes with their hot flashes, we often choose a trial of a low-dose antidepressant, either an SSRI or SNRI. One drug is approved by the US Food and Drug Administration (FDA) for the treatment of hot flashes (but not for mood disorder). This is low-dose salt of paroxetine, 7.5 mg/d, which has the advantage of exerting no adverse effect on libido or weight (but is sometimes difficult to obtain because it is a branded product that might not be covered, or not covered fully, by a given patient's insurance plan). Other antidepressants can be used in doses lower than needed for depression, with more rapid onset of effect on hot flashes, often within 2 weeks.

Last, transdermal clonidine, an antihypertensive, also has been found to relieve hot flashes.

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CONTINUED FROM PAGE 18

Not a recommended strategy: Systemic hormone therapy

Although hormone therapy is, in general, the gold standard for alleviating hot flashes, it is contraindicated in most women with breast cancer.[4] At our institution, we avoid systemic hormone therapy for hot flashes in almost all breast cancer patients.

CASE 2

Sarah first presented with hot flashes that improved while taking escitalopram 10 mg. Her night sweats persisted, however. Gabapentin 300 mg was added to take nightly. With this regimen, she finally felt that she was coping better. Six months later, she reported that she and her long-term partner had not been able to resume vaginal intercourse post–breast cancer treatment because of pain.

The challenge of managing GSM

What if your patient says, "Doctor, I'm really doing OK with my hot flashes, but sex has become painful. I don't have any interest. I have vaginal dryness, and it's affecting my quality of life"?

Studies have shown that GSM affects up to 50% of women, and even more than that among women who have had breast cancer.[5] The condition interferes with sexual intimacy, disrupts quality of life, and can sour a partnership—significant quality-of-life concerns for breast cancer survivors.

For mild symptoms, encourage patients to apply a lubricant just before intercourse or a vaginal moisturizer twice weekly; moisturizers improve vaginal pH, too. These treatments do not fix the problem of a lack of superficial cells due to estrogen loss, however; to accomplish that, consider prescribing low-dose vaginal estrogen therapy or intravaginal dehydroepiandrosterone (DHEA). This strategy is felt to be safe for many breast cancer survivors, as systemic absorption of estrogen is minimal if dosed low, keeping levels in the postmenopausal range.

The American College of Obstetricians and Gynecologists (ACOG), the North American Menopause Society (NAMS), and the Endocrine Society agree that vaginal estrogen therapy may be a good option for many women with breast cancer for whom moisturizers and lubricants are inadequate.[6] Delivery options include vaginal creams, tablets, suppositories used 2 or 3 times per week, or the low-dose vaginal estrogen ring, replaced every 3 months. We are concerned about using vaginal estrogen in women who have had aromatase inhibitor (AI) therapy; their estrogen levels are so low that absorbing even a small amount might make a difference in terms of effectiveness of AI. For women who need more than lubricants or vaginal moisturizers, particularly those taking anti-estrogen therapy (aromatase therapy), the use of low-dose vaginal hormones may be considered on an individual basis, but should include the oncologist in decision making.[1,3]

Beyond low-dose vaginal estrogen therapies, there are additional options that can be considered but with less supporting data for treating GSM in women with breast cancer.

Oral ospemifene, a selective estrogen-receptor modulator (SERM; Osphena), might be neutral or even protective in its effect on the breast, as demonstrated in preclinical trials.[7] In human trials, the drug is approved only for painful intercourse, not for loss of libido, and has not been tested in breast cancer patients.

Intravaginal DHEA (Prasterone), has been on the market for almost 1 year. The drug is approved for treating painful intercourse, but it also reverses vaginal atrophy and alleviates urinary symptoms. Because DHEA is a prohormone, it is converted to estrogen and androgen in the vagina. Again, absorption appears minimal. Intravaginal DHEA does not have the US Food and Drug Administration (FDA) black-box warning that vaginal estrogen products do, but it is accompanied by a warning that it has not been tested in women with breast cancer.

Tissue selective estrogen receptor modulator is a conjugated estrogen combined with a third-generation SERM bazedoxifene, which treats hot flashes and reverses vaginal atrophy. This new systemic agent is probably neutral on the breast (at least that is the finding in clinical trials at 2 years[8]); again, how-

CONTINUED ON PAGE 35

FAST TRACK

Although not well tolerated in breast cancer patients, reassure your patient of the many available and on-the-horizon treatments for their menopause symptoms

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BREAK THIS PRACTICE HABIT

Health care costs matter to patients, and we can do something about it

Incorporate thoughtful use of cost-effective products and tests, and innovative care redesign, into your practice to align with the principles of high-value care delivery

Lauren D. Demosthenes, MD

IN THIS ARTICLE

CASE 1 Huge out-of-pocket cost makes patient forego treatment

Ms. M. is a 28-year-old patient who recently posted this on her Facebook page: "I went to the drugstore this morning to pick up a prescription, and as the pharmacist handed it to me she said, 'That will be $180.00.' And that's after insurance coverage! Wow! I think I'll pass!"

Our patients probably experience this type of situation more commonly than we know.

CASE 2 Catastrophic medical costs bankrupt family

A middle-class couple who had college degrees and full-time jobs with health insurance had twins at 24 weeks' gestation. They accrued $450,000 in medical debt after exceeding the $2 million cap of their insurance policy. Having premature twins cost them everything. They liquidated their retirement and savings accounts, sold everything they had, and still ended up filing for bankruptcy.[1]

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The author reports no financial relationships relevant to this article.

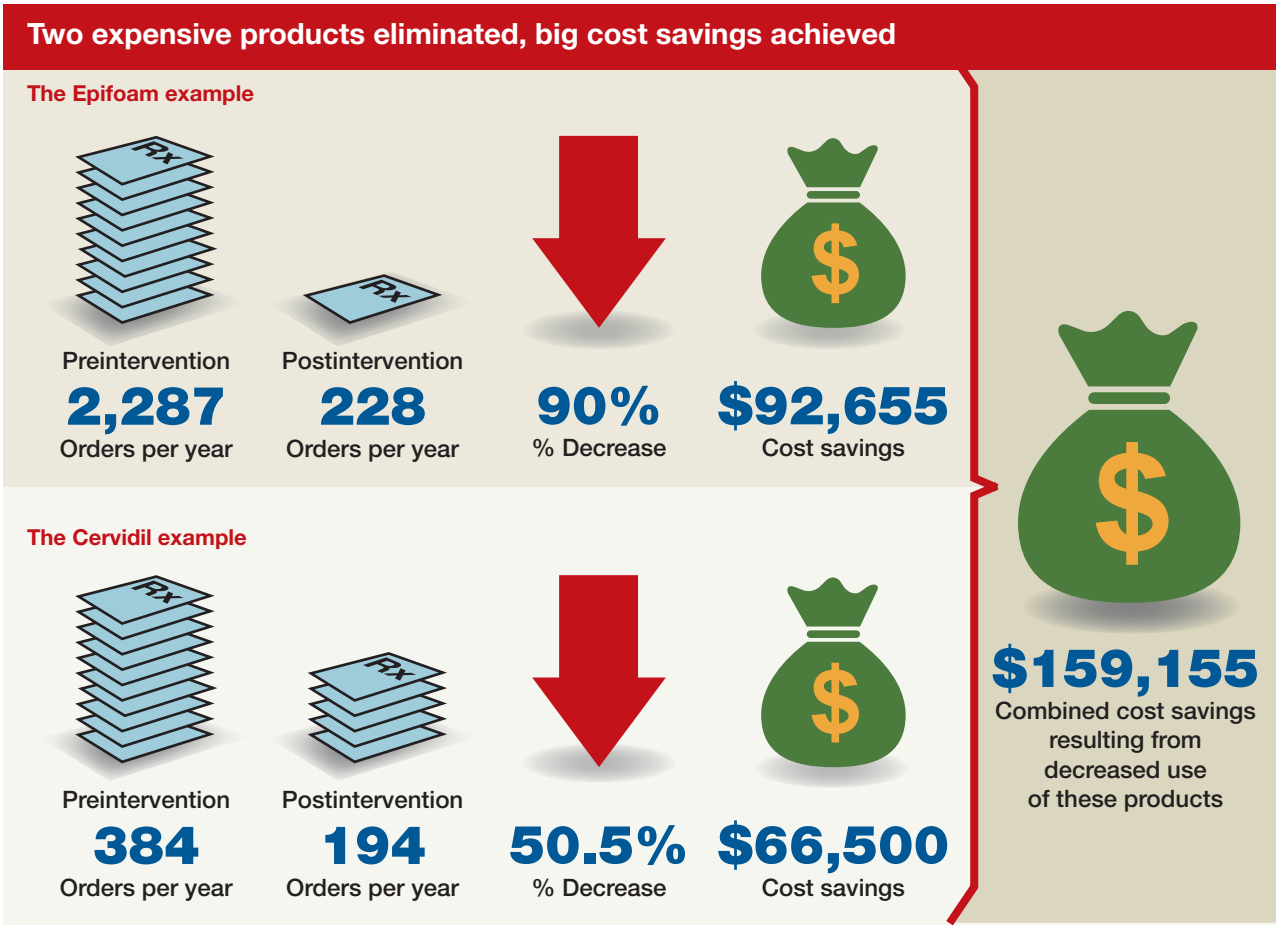
Costs indeed matter to patients, and we have a professional responsibility to help our patients navigate the murky waters of health care so that they can maintain financial as well as physical health.

Rising costs, lower yield, and opportunities for change

Rising health care costs are unsustainable for both our patients and our society. Although the United States spends more on health care than any other developed country, our health outcomes are actually worse—ranking at or near the bottom in both prevalence and mortality for multiple diseases, risk factors, and injuries.[2]

Of the 171 countries included in a study by the United Nations Maternal Mortality Estimation Inter-Agency Group, the United States was 1 of 13 countries that had an increasing maternal mortality and the only developed nation with an increasing maternal mortality rate.[3] This tells us that, as our country spends more on health care, our patients' health is not improving. For individuals, medical bills are now the leading cause of personal bankruptcy in the United States, even for those who are insured.[4]

ObGyns play an important leadership role in the practice of cost-conscious health care, as 25% of hospitalizations in the United States are pregnancy related.[5,6] In addition, the wide scope of ObGyn practice reaches



beyond pregnancy-related conditions and provides multiple opportunities to decrease the use of unnecessary tests and treatments.

The good news is that approximately 30% of health care costs are wasted on unnecessary care that could be eliminated without decreasing the quality of care.[7]

High-value change #1: Eliminate use of expensive products

Embarking on a high-value care improvement project, experts at Greenville Health System examined the cost of different topical pain medications for perineal pain after a vaginal delivery. They found that Epifoam (hydrocortisone acetate/pramoxine hydrochloride) was ordered 2,287 times over the course of a year.

The study intervention consisted of an educational grand rounds and discussion of a Cochrane review, which concluded there was no difference in pain relief with topical anesthetics compared with placebo.[8] Less expensive options for pain relief were discussed, and the department agreed to remove Epifoam as a standing order.

After the intervention, Epifoam was ordered 228 times, a 90% reduction. Over the period of a year, this translated to a cost savings of $92,655 for the hospital, with reduced charges passed on to patients.[9] Thus, a seemingly small individual cost ($45.00 per can of Epifoam) can add up to a substantial sum in a large health care system.

Similarly, practitioners were educated about options for cervical ripening and were given information on the cost and efficacy of various cervical ripening agents. A Cochrane review found that oral misoprostol is as effective as vaginal misoprostol and results in fewer cesarean deliveries than vaginal dinoprostone (Cervidil).[10] Practitioners

were asked to consider making the transition to oral misoprostol. This action resulted in a 50.5% decrease in Cervidil use, from 384 to 194 cases, producing a cost savings of $66,500. The following year, the department removed Cervidil from the formulary as a high-value decision.[9]

Both of these examples illustrate what a value-minded department can accomplish by implementing performance improvement projects that focus on high-value care.

High-value change #2: Stop ordering unnecessary lab work

Another high-value change to consider: Examine each laboratory test order to understand if the test results will really alter the care of a patient. Providers vary, and ordering lab tests to "make sure" can add up as financial expense.

Best practices from the American College of Obstetricians and Gynecologists (ACOG) and other professional societies can help guide decision-making as we order lab tests. Think twice, for example, about whether every evaluation for preeclampsia requires a uric acid test, since ACOG does not endorse that as part of the diagnostic criteria. While a single uric acid test costs only $8.00 to $38.00 (according to Healthcare Bluebook), testing uric acid in many patients over the course of a year can add up to significant dollars.[11]

High-value change #3: Consider care redesign

In addition to seeking opportunities to use more cost-effective products and reduce the use of unnecessary tests, "care redesign" is an innovative way to provide high-quality care (and increased patient satisfaction) at a lower cost for both the health care system and the patient. A prime example of care redesign is using telehealth to enhance prenatal care.

Several health systems around the country are piloting and implementing remote blood pressure monitoring, app-based prenatal education, and telehealth visits to enhance prenatal care.[12,13] Use of a home blood pressure monitor can reduce in-person visits for low-risk prenatal care and open up access for other patients. Additionally, allowing the patient to participate in her own care at home or work can eliminate drives to and waits in the office and reduce absence from work because of a doctor visit.

A systematic review of more than 60,000 women showed that low-risk women who attend 5 to 9 prenatal visits have the same outcomes as women who attend the standard schedule of 13 to 15 visits.[14] Although patient satisfaction was higher with more visits, when a bidirectional app or a telehealth visit is offered as an option, then patient satisfaction is equivalent to that in the standard schedule group.[12] So why not expand the choice for patients?

FAST TRACK

Care redesign is an innovative way to provide high-quality care and increased patient satisfaction at a lower cost for both the health care system and the patient

The challenge of teaching high-value care: Medical education responds

In a 2010 article in the *New England Journal of Medicine,* Dr. Molly Cooke commented on medical education's responsibility regarding cost consciousness in patient care, and she highlighted the importance of teaching medical students and residents about considering cost in treating patients.[15] Similarly, the Accreditation Council for Graduate Medical Education asks residents to consider cost and stewardship of medical resources as one of its system-based practice competencies.[16] In 2012, the Choosing Wisely campaign, initiated by the American Board of Internal Medicine Foundation, asked specialty society members to identify tests or procedures commonly used in their field whose necessity should be questioned and discussed.[17] ACOG and other women's health specialty societies participate in this campaign.

From an educational standpoint, ACOG's Council on Resident Education in Obstetrics and Gynecology has developed a curriculum resource, "Cases in High Value Care," that can be used by any women's health department to start the conversation on high-value care.[18] The web program encourages medical students and residents to submit clinical vignettes that demonstrate examples of low- and high-value care. These cases can be used

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for discussion and debate and can serve as high-value care performance improvement projects in your own department.

Other useful publications are available outside the ObGyn specialty. Consider the Society of Hospital Medicine's article series in the *Journal of Hospital Medicine*, "Choosing Wisely: Things We Do for No Reason"and "Choosing Wisely: Next Steps in Improving Healthcare Value."[19] The former focuses on discussing practices (tests, procedures, supplies, and prescriptions) that may be poorly supported by evidence or are part of standard practice even though other less expensive, higher-value alternatives may be available. The latter highlights perspective pieces that describe health care value initiatives relating to the practice of hospital medicine.

The bottom line

ObGyns and other health care providers are concerned about providing high-value care to patients and are working toward improving performance in this area. We really do care about the health care–related financial burdens that confront Ms. M., the premature twins' parents, and all our patients. ●

FAST TRACK

ObGyns care about the health care–related financial burdens confronting patients and are working to improve providing high-value care

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With this article we debut a new series, "Break This Practice Habit," spearheaded by Dr. Lauren Demosthenes, who makes overarching high value cost decisions in her role as Medical Director of High Value Care and Innovation, Department of ObGyn at Greenville Health System in Greenville, South Carolina. Watch for quarterly case presentations of low value, low evidence practices that should be questioned in current day, followed by reasons why that practice should be abandoned. If you would like to contribute to this series, please submit your query to Dr. Demosthenes at ldemosthenes@mdedge.com. Watch next time for an examination of the practice of uterine aspiration in the operating room, and read the authors' argument as to why it should be moved to the office setting.

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Should we abandon minimally invasive surgery for cervical cancer?

Recent data infer that, as a specialty, we should consider an open surgical approach

Mary M. Mullen, MD, and David G. Mutch, MD

A minimally invasive approach for gynecologic surgery increasingly has become the surgical modality of choice (vs open surgery) due to decreased perioperative and postoperative morbidity for many gynecologic cancers.[1-3] This has included radical hysterectomy for cervical cancers. Until recently, retrospective evidence supported its use, suggesting decreased perioperative and postoperative complications with similar survival outcomes between patients undergoing minimally invasive and open radical hysterectomy.[4,5] In November 2018, two new studies were published in the *New England Journal of Medicine,* and another study was presented at the American Society of Clinical Oncology (ASCO) annual meeting challenging this practice paradigm. These studies reveal a higher risk of disease recurrence and decreased overall survival with minimally invasive surgery (MIS) compared with open surgery for Stages IA–IB1 cervical cancer. These findings have resulted in a change in practice nationwide.

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The authors report no financial relationships relevant to this article.

RCT findings astonish specialty

The first study, the Laparoscopic Approach to Cervical Cancer (LACC) trial, authored by Ramirez and colleagues was a noninferiority randomized controlled trial evaluating MIS versus open radical hysterectomy for patients with cervical cancer (Stage 1A–1B1) conducted from 2008–2017.[6] The primary outcome was disease-free survival at 4.5 years. Secondary outcomes included recurrence and overall survival rates. Power analysis suggested a sample size of 740 patients to provide greater than 80% power with a noninferiority margin of -7.2% between disease-free rates of the two groups. However, the study was closed prematurely at enrollment of 631 patients (85% recruitment) by the Data Safety Monitoring Committee due to the astounding differences in survival between the two groups.

The rate of disease-free survival at 4.5 years was 86.0% with MIS and 96% with open surgery. There were 27 recurrences (8.5%) in the MIS group and only 7 (2.2%) in the open-surgery group, accounting for a hazard ratio (HR) for disease recurrence or death from cervical cancer of 3.74 (95% confidence interval [CI], 1.63–8.58). This difference remained after adjusting for confounding variables. There were 22 deaths—19 (5.9%) in the

IN THIS ARTICLE

MIS group and 3 (0.1%) in the open-surgery group (HR, 6.56). Although patient characteristics between groups appeared to be similar, more than one-third of patients in each group had missing data regarding histology at the time of surgery, grade, tumor size, lymphovascular space invasion, and depth of invasion. Interestingly, intraoperative, perioperative, and postoperative complications between the two groups were similar (with rates of 11%, about 40%, and about 25%, respectively).

Surprising findings continue in *NEJM*

The second study, by Melamed and colleagues, was a retrospective cohort study using data from the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database evaluating women with stage IA2 or IB1 cervical cancer who underwent either minimally invasive or open radical hysterectomy between 2010 and 2013.[7] The primary outcome was time to death.

Participant characteristics. A total of 2,461 women were included: 49.8% underwent MIS and 50.2% underwent open surgery. According to the raw data, patients undergoing MIS were more likely to be white, privately insured, reside in an area associated with higher income, undergo surgery at a nonacademic institution, have adenocarcinoma, and have smaller, lower-grade tumors. After propensity-score weighting, demographic and clinical characteristics were similar between groups. Median follow-up was 45 months.

Results. A total of 164 deaths occurred: 94 in the MIS and 70 in the open-surgery group. The risk of death during study follow-up was 9.1% in the MIS group versus 5.3% in the open-surgery group, and women who underwent MIS had shorter overall survival (P = .002; HR, 1.65; 95% CI, 1.22–2.22). Mortality rates remained higher in the MIS group after adjusting for adjuvant therapy (HR, 1.62; 95% CI, 1.2–2.19). However, the HR for death with MIS was not statistically significant in a subgroup analysis evaluating tumors 2 cm in size or less (HR, 1.46; 95% CI, 0.70–3.02). The authors demonstrated that the adoption of MIS for radical hysterectomy corresponded to a drop in the 4-year survival rate of 0.8% per year (P = .01).

FAST TRACK

Recent findings from an RCT, a retrospective study, and data presented at ASCO are consistent that an open approach is superior to MIS for cervical cancer

ASCO meeting data emphasize lower mortality and survival rates for MIS

A third important, but less publicized study, is a retrospective cohort study by Marguland and colleagues that was presented at the ASCO annual meeting and is pending publication. This study evaluated the 5-year survival of women with stage IB1 cervical cancer after MIS or open radical hysterectomy from 2010 to 2013.[8] The findings demonstrated similar results to the above studies with decreased 5-year survival rates in patients with a tumor size of 2 cm or greater in the MIS group (81.3% vs 90.8; HR, 2.14; 95% CI, 1.36–3.38; P<.001). These results hold true when controlling for confounding clinical variables. Interestingly, in a subset analysis evaluating patients with tumors less than 2 cm, survival rates were similar between groups. This study confirms decreased morbidity and cost associated with MIS radical hysterectomy.

A consistent message emerges from 3 independent studies

We must take the study findings seriously and evaluate the quality of the evidence. There are many strengths to the above studies. First and most importantly, the LACC study is the only prospective randomized controlled trial (RCT) to evaluate this very important clinical question. RCTs are the gold standard for understanding the effectiveness and safety of an intervention compared with an established treatment. The study was well designed in that the study population was clearly defined with detailed inclusion and exclusion criteria. The intention to treat analysis was similar to the per-protocol analysis, and the study followed Consolidated Standards of Reporting Trials (CONSORT) guidelines. While the study was stopped early, there was still 84%

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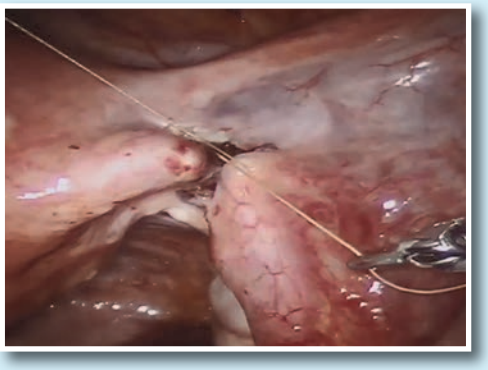

Robot-assisted laparoscopic tubal anastomosis following sterilization

Patricia J. Mattingly, MD; Arielle R. Gumer, MD; and Arnold P. Advincula, MD

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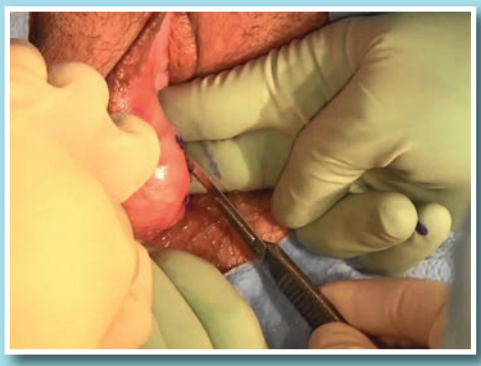

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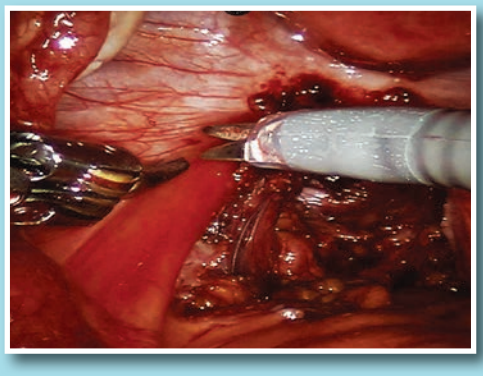
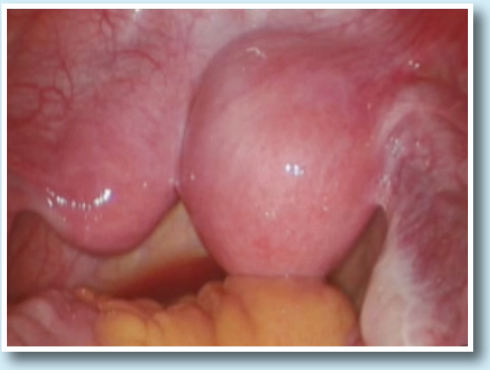


Robot-assisted laparoscopic excision of a rectovaginal endometriotic nodule

Obianuju Sandra Madueke-Laveaux, MD, MPH; Khara M. Simpson, MD; and Arnold P. Advincula, MD

OBG Manag. 2017;29(4):42.



Robot-assisted laparoscopic resection of a noncommunicating cavitary rudimentary horn

Obianuju Sandra Madueke-Laveaux, MD, MPH; Beth W. Rackow, MD; and Arnold P. Advincula, MD

OBG Manag. 2017;29(1):51.

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CONTINUED FROM PAGE 30

power for the primary outcome. Therefore, when it comes to MIS for cervical cancer, this study provides the soundest data we have available. It is also extremely noteworthy that two additional large retrospective studies evaluating this question separately found similar results.

Criticisms remain, but older research has drawbacks

A main concern with these studies is that the findings challenge previously published research, which overall suggest similar survival outcomes between MIS and open surgical approaches. However, in evaluating the previously published retrospective data it is clear that the studies have considerable limitations.

Long-term survival not always evaluated in research. First, the majority of studies comparing MIS and open treatment modalities specifically evaluated perioperative complications and did not consider long-term survival.[4,9,10] Of those studies that did consider survival outcomes, the groups often were not balanced and were skewed toward the open surgery patients having larger tumors and higher-stage disease.[5]

Difficult to compare "apples to apples." These findings are complicated by the fact that open radical hysterectomies were essentially replaced by MIS radical hysterectomies, and therefore, the comparisons are not equivalent since they are comparing different treatment times. For instance, throughout the time period many of these studies were conducted, the treatment paradigm for early-stage cervical cancer changed regarding who received adjuvant therapy and imaging techniques. Therefore, these studies are not comparing apples to apples.[11,12]

Are we going to increase morbidity? Another common concern when considering abandoning MIS for cervical cancer is the increase in morbidity that our patients may incur immediately postoperatively due to open surgery. Multiple studies have associated minimally invasive radical hysterectomies with decreased blood loss, shorter hospital stay, lower transfusion rates, and decreased time until return of bowel function.[4,10,13]

While we recognize that open surgery is associated with increased morbidity, we do argue that, with the almost-universal implementation of Enhanced Recovery Pathways (ERP) in gynecologic oncology, the disparities between the two groups will be minimized and likely are much smaller than that reported in historical literature.[14] Notably, there were no differences in peri-, intra-, or postoperative complications between the two groups in the LACC study, indicating that MIS may not be saving our patients as much morbidity as we think.

Surgical ability differences. Despite the vast strengths associated with the studies we have discussed they certainly embody limitations as well. First, surgical aptitude is difficult to evaluate and tease out. This is extremely pertinent given perioperative, and postoperative, outcomes in cervical cancer, as well as survival outcomes, in multiple surgically managed cancers, which are directly associated with the volume and proficiency of the surgeon.[15-19] Additionally, the mode of minimally invasive surgery that was most commonly utilized was different from practice in the United States. Eighty four percent of the patients in the MIS group of the LACC study underwent laparoscopic and 13.6% underwent robot-assisted radical hysterectomy. This is starkly different from US practice, where 75% of gynecologic oncologists report performing radical hysterectomies only robotically.[20]

FAST TRACK

Although previously published research show similar survival rates for open and MIS approaches, those data are lacking and retrospective

Take-home points

Consider this latest evidence in your surgical planning. Most importantly, the evidence is the evidence. In other words, we can attempt to explain away the findings, but despite arguments against these studies, these data are the most reliable evidence we have to date regarding outcomes for cervical cancer with MIS versus open approaches. These data demonstrate that MIS may be harming our patients and so we must take this into careful consideration during surgical planning.

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For small cancers, MIS may be the best option. MIS radical hysterectomy may still be the best approach for patients with tumors less than 2 cm in size. The LACC study is not powered to evaluate oncologic outcomes in this subset of patients and the two retrospective studies suggest no difference in survival in this cohort.

We must work to understand the driving force between the disparate outcomes. Are the increased rates due to the open surgical approach, the uterine manipulator, circulating CO2 gas, or tumor exposure to the intraperitoneal cavity as the authors suggest? Or is it due to surgical expertise, tumor biology, tumor size, or mode of MIS? At this point the impelling cause is unknown.

New NCCN guidelines are to come. Up to this point the National Comprehensive Cancer Network (NCCN) guidelines stated that "radical hysterectomy procedure may be performed either via laparotomy or laparoscopy." Given these recent studies, however, new NCCN guidelines will be released cautioning the use of the MIS approach. In short, these data have transformed the standard of care.

At our institution, the majority of radical hysterectomies will be performed open. Continued discussion remains regarding small lesions, but even in these cases most surgeons will proceed with open surgery in an attempt to maximize survival.

As providers, it is our duty to honestly reflect on published data and comprehensively counsel patients about the risks and benefits associated with each approach, including the fact that recurrence may be higher with a minimally invasive approach. Patients and providers must then collectively decide what is best for each individual case. ●

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ever, it has not been tested in patients with breast cancer.

Nonhormone therapies

Topical lidocaine for insertional dyspareunia has been studied in postmenopausal women with breast cancer with severe GSM, dyspareunia, increased sexual distress scores, or abnormal sexual function with improvement seen using 4% aqueous lidocaine versus saline applied with a cotton ball to the vestibule for 3 minutes before vaginal penetration.[9]

Vaginal laser therapy has the potential to ameliorate distressing GSM without the need for local hormone intervention; however, placebo or active-controlled trials and long-term safety follow-up are needed.[5]

Treatment begins with a conversation

Most importantly, we need to listen to our patients in discomfort because of their menopausal symptoms. Consider proceeding along these lines: "You've been treated for breast cancer; now, let's look at the medical issues that are affecting your quality of life. Are you depressed? Are you having hot flashes? Are you getting enough sleep? Have you stopped having sex or not restarted after your breast cancer treatment? Are you having painful sex or avoiding sex due to fear of pain? Let's discuss options and work with your oncologist to try to relieve your symptoms and make your life better."

First-line therapy for the treatment of menopausal symptoms in women with a history of breast cancer should start with lifestyle changes and nonhormone therapies. For GSM, lubricants and vaginal moisturizers should be tried first and may be effective. Reassure patients that there are many treatment options, even though not all of them have been well-tested in breast cancer patients, and that new modalities are under investigation and review (see "Newly arrived and on the horizon," page 18). Become familiar with published data on the safety and effectiveness of the range of available treatments; guide patients through the process of finding what works best for them; and invite their oncologist into the therapeutic partnership. If you do not feel comfortable with these issues in women who are breast cancer survivors, find a menopause specialist to help, available by zip code at Find a Provider, http://www.menopause.org. ●

FAST TRACK

For a list of menopause specialists, visit menopause.org

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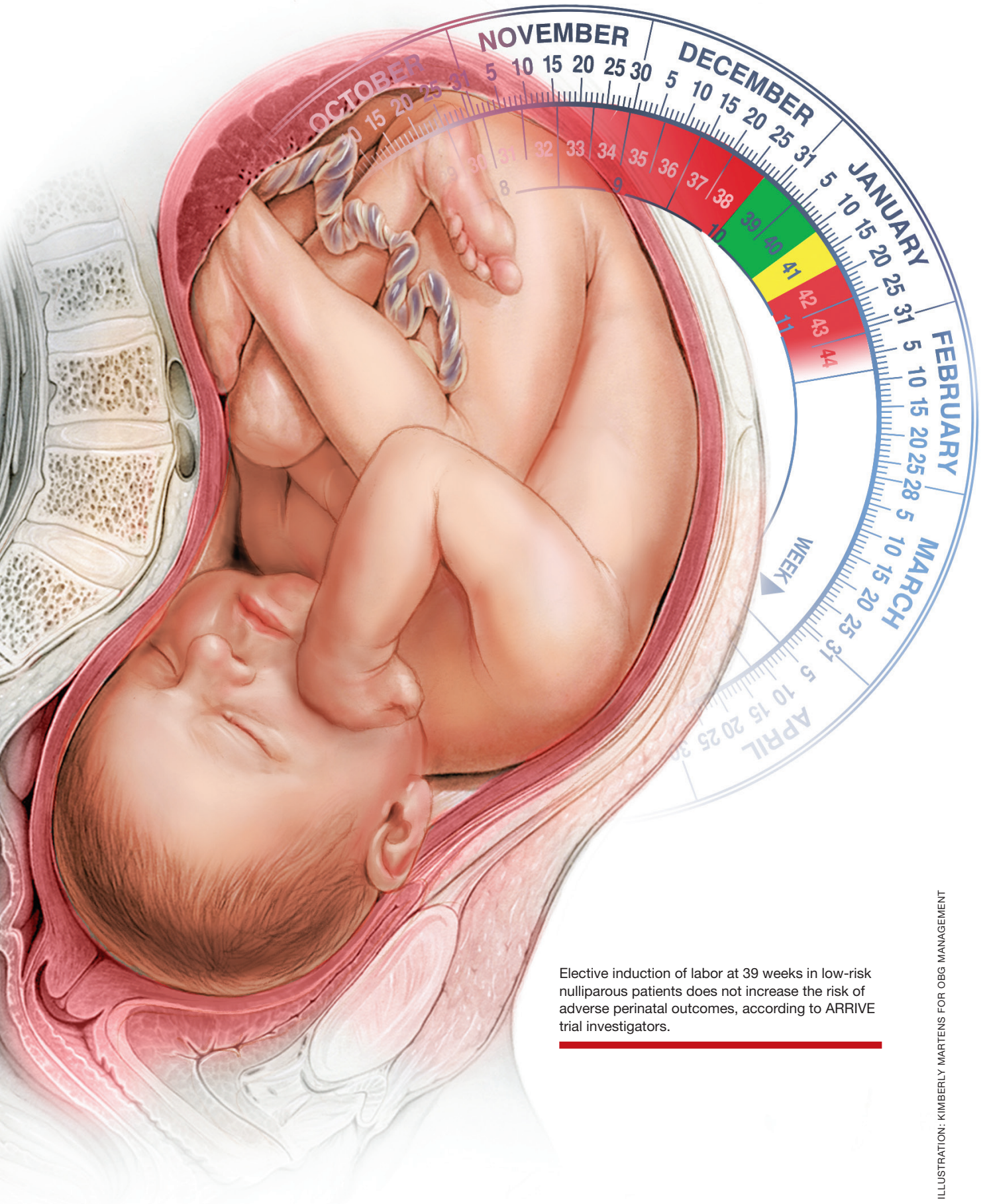

Elective induction of labor at 39 weeks in low-risk nulliparous patients does not increase the risk of adverse perinatal outcomes, according to ARRIVE trial investigators.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

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The author reports no financial relationships relevant to this article.

What are the clinical implications of trial results on these 2 delivery-related issues: timing of elective induction of labor and timing of pushing in the second stage? Plus, ACOG's new recommendations for optimizing postpartum care.

The past year was an exciting one in obstetrics. The landmark ARRIVE trial presented at the Society for Maternal-Fetal Medicine's (SMFM) annual meeting and subsequently published in the *New England Journal of Medicine* contradicted a long-held belief about the safety of elective labor induction. In a large randomized trial, Cahill and colleagues took a controversial but practical clinical question about second-stage labor management and answered it for the practicing obstetrician in the trenches. Finally, the American College of Obstetricians and Gynecologists (ACOG) placed new emphasis on the oft overlooked but increasingly more complicated postpartum period, offering guidance to support improving care for women in this transitional period.

Ultimately, this was the year of the *patient,* as research, clinical guidelines, and education focused on how to achieve the best in safety and quality of care for delivery planning, the delivery itself, and the so-called fourth trimester.

IN THIS ARTICLE

ARRIVE: Labor induction at 39 weeks reduces CD rate with no difference in perinatal death or serious outcomes

Grobman WA, Rice MM, Reddy UM, et al; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med. 2018;379:513-523.

The term "elective induction of labor" has long had a negative connotation because of its association with increased CD rates and adverse perinatal outcomes. This view was based on results from older observational studies that compared

outcomes for labor induction with those of spontaneous labor. In more recent observational studies that more appropriately compared labor induction with expectant management, however, elective induction of labor appears to be associated with similar CD rates and perinatal outcomes.

To test the hypothesis that elective induction would have a lower risk for perinatal death or severe neonatal complications than expectant management in low-risk nulliparous women, Grobman and colleagues conducted A Randomized Trial of Induction Versus Expectant Management (ARRIVE).[1]

Study population, timing of delivery, and trial outcomes

This randomized controlled trial included 6,106 women at 41 US centers in the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Study participants were low-risk nulliparous women with a singleton vertex fetus who were randomly assigned to induction of labor at 39 to 39 4/7 weeks (n = 3,062) or expectant management (n = 3,044) until 40 5/7 to 42 2/7 weeks.

"Low risk" was defined as having no maternal or fetal indication for delivery prior to 40 5/7 weeks. Reliable gestational dating was required.

While no specific protocol for induction of labor management was required, there were 2 requests: 1) Cervical ripening was requested for an unfavorable cervix (63% of participants had a modified Bishop score <5), and 2) a duration of at least 12 hours after cervical ripening, rupture of membranes, and use of uterine stimulant was requested before performing a CD for "failed induction" (if medically appropriate).

The primary outcome was a composite of perinatal death or serious neonatal complications. The main secondary outcome was CD.

Potentially game-changing findings

The investigators found that there was no statistically significant difference between the elective induction and expectant management groups for the primary composite perinatal outcome (4.3% vs 5.4%; P = .049, with P<.046 prespecified for significance). In addition, the rate of CD was significantly lower in the labor induction group than in the expectant management group (18.6% vs 22.2%; P<.001).

Other significant findings in secondary outcomes included the following:

- Hypertensive disorders of pregnancy were significantly lower in the labor induction group compared with the expectant management group (9.1% vs 14.1%; P<.001).
- The labor induction group had a longer length of stay in the labor and delivery unit but a shorter postpartum hospital stay.
- The labor induction group reported less pain and more control during labor.

Results refute negative notion of elective labor induction

The authors concluded that in a low-risk nulliparous patient population, elective induction of labor at 39 weeks does not increase the risk for adverse perinatal outcomes and decreases the rate of CD and hypertensive disorders of pregnancy. Additionally, they noted that induction at 39 weeks should not be avoided with the goal of preventing CD, as even women with an unfavorable cervix had a lower rate of CD in the induction group compared with the expectant management group.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

After publication of the ARRIVE trial findings, both ACOG and SMFM released statements supporting elective labor induction at or beyond 39 weeks' gestation in low-risk nulliparous women with good gestational dating.[2,3] They cited the following as important issues: adherence to the trial inclusion criteria except for research purposes, shared decision-making with the patient, consideration of the logistics and impact on the health care facility, and the yet unknown impact on cost. Finally, it should be a priority to avoid the primary CD for a failed induction by allowing a longer latent phase of labor, as long as maternal and fetal conditions allow.

In my practice, I actively offer induction of labor to most of my patients at 39 weeks after a discussion of the risks and benefits.

Immediate pushing in second stage offers benefits and is preferable to delayed pushing

Cahill AG, Srinivas SK, Tita AT, et al. Effect of immediate vs delayed pushing on rates of spontaneous vaginal delivery among nulliparous women receiving neuraxial analgesia: a randomized clinical trial. JAMA. 2018;320:1444-1454.

In a randomized trial of 2,414 women, Cahill and colleagues sought to answer a seemingly simple question: What is the best timing for pushing during the second stage of labor—immediate or delayed?

Practical management of the second stage of labor (defined as complete cervical dilation to the delivery of the infant) varies by provider and setting, and previous data on pushing efforts are conflicting. Delayed pushing, or "laboring down," has been suggested to allow passive fetal rotation and to conserve maternal energy for pushing. Older studies have shown that delayed pushing decreases the rate of operative delivery. More recent study data have not demonstrated a difference between immediate and delayed pushing techniques on vaginal delivery rates and have noted that increased maternal and neonatal morbidities are associated with a longer second stage of labor.

The recent trial by Cahill and colleagues was designed to determine the effect of these 2 techniques on spontaneous vaginal delivery rates and on maternal and neonatal morbidities.[4]

Large study population

This randomized pragmatic trial was conducted at 6 centers in the United States. Study participants (2,404 women completed the study) were nulliparous women at 37 or more weeks' gestation with neuraxial anesthesia who were randomly assigned at complete cervical dilation either to immediate pushing (n = 1,200) or to delayed pushing, that is, instructed to wait 60 minutes before starting to push (n = 1,204). The obstetric provider determined the rest of the labor management.

The primary outcome was the rate of spontaneous vaginal delivery. Secondary outcomes included duration of the second stage of labor, duration of active pushing, operative vaginal delivery, CD, and several maternal assessments (postpartum hemorrhage, chorioamnionitis, endometritis, and perineal lacerations).

Both groups had similar vaginal delivery rates, differences in some measures

There was no difference in the primary outcome between the 2 groups: The spontaneous vaginal delivery rate was 85.9% (n = 1,031) in the immediate pushing group and 86.5% (n = 1,041) in the delayed pushing group ($P = .67$).

Analysis of secondary outcomes revealed several significant differences:

- decreased total time for the second stage of labor in the immediate pushing group compared with the delayed pushing group (102.4 vs 134.2 minutes) but longer active pushing time (83.7 vs 74.5 minutes)
- a lower rate of postpartum hemorrhage, chorioamnionitis in the second stage, neonatal acidemia, and suspected neonatal sepsis in the immediate pushing group
- a higher rate of third-degree perineal lacerations in the immediate pushing group.

No difference was found between groups in rates of operative vaginal deliveries, CDs, endometritis, overall perineal lacerations, or spontaneous vaginal delivery by fetal station or occiput position.

Authors' takeaway

The authors concluded that since delayed

FAST TRACK

In nulliparous women with neuraxial anesthesia assigned to either immediate pushing or delayed pushing, there was no difference in the spontaneous vaginal delivery rate—85.9% vs 86.5%, respectively

WHAT THIS EVIDENCE MEANS FOR PRACTICE

After reviewing the available literature in light of this study's findings, ACOG released a practice advisory in October 2018 stating that "it is reasonable to choose immediate over delayed pushing in nulliparous patients with neuraxial anesthesia."[5] Nulliparous patients with neuraxial anesthesia should be counseled that delayed pushing does not increase the rate of spontaneous vaginal birth and may increase both maternal and neonatal complications. As this may be a practice change for many obstetrics units, the obstetric nursing department should be included in this education and counseling.

In my practice, I would recommend immediate pushing, but it is important to include both the patient and her nurse in the discussion.

pushing does not increase spontaneous vaginal delivery rates and increases the duration of the second stage of labor and both maternal and neonatal morbidity, immediate pushing may be preferred in this patient population.

ACOG aims to optimize postpartum care

FAST TRACK

Postpartum care plans should be started before birth, during regular prenatal care, and adjusted in the hospital as needed

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 736. Optimizing postpartum care. Obstet Gynecol. 2018;131:e140-e150.

In May 2018, ACOG released "Optimizing postpartum care," a committee opinion that proposes a new model of comprehensive postpartum care focused on improving both short- and long-term health outcomes for women and infants. (This replaces the June 2016 committee opinion No. 666.) Described as "the fourth trimester," the postpartum period is a critical transitional period in which both pregnancy-related and pre-existing conditions may affect maternal, neonatal, and family status; half of pregnancy-related maternal deaths occur during the postpartum period.[6]

The postpartum visit: Often a lost opportunity

ACOG cites that up to 40% of women in the United States do not attend their postpartum visit.[6] Many aspects of the postpartum visit, including follow-up for chronic diseases, mental health screening, and contraceptive counseling, provide opportunities for acute intervention as well as establishment of healthy behaviors. Some studies have shown that postpartum depression, breastfeeding, and patient satisfaction outcomes improve as a result of postpartum engagement.

ACOG's recommendations

Ongoing process. ACOG's first proposed change concerns the structure of the postpartum visit itself, which traditionally has been a single visit with a provider at approximately 6 weeks postpartum. Postpartum care plans actually should be started before birth, during regular prenatal care, and adjusted in the hospital as needed so that the provider can educate patients about the issues they may face and resources they may need during this time. This prenatal preparation hopefully will encourage more patients to attend their postpartum visits.

Increased provider contact. Another proposed change is that after delivery, the patient should have contact with a provider within the first 3 weeks postpartum. For high-risk patients, this may involve

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Postpartum care should be seen as an ongoing process to address both short- and long-term health outcomes for the patient, her newborn, and their family. This process should begin with planning in the antenatal period, continue with close individualized follow-up within the first 3 weeks of birth, and conclude with a comprehensive postpartum evaluation and transition to well-woman care. Shifting the paradigm of postpartum care will take considerable commitment and resources on the part of obstetric providers and their practices.

In my practice, we routinely see hypertensive patients within the first week postpartum and patients at risk for postpartum depression within the first 2 weeks in our clinics. We have a standard 6-week postpartum visit for all patients as well. Going forward, we need to further determine how and when we can implement ACOG's extensive new recommendations for optimizing postpartum care.

FAST TRACK

ACOG's proposed changes will require education and resources, a significant increase in obstetric provider time and effort, and consideration of policy change on such issues as parental leave and postpartum care reimbursement

an in-person clinic visit as soon as 3 to 10 days postpartum (for hypertensive disorders of pregnancy) or at 1 to 2 weeks (for postpartum depression screening, incision checks, and lactation issues). For lower-risk patients, a phone call may be appropriate and/or preferred. Ongoing follow-up for all patients before the final postpartum visit should be individualized.

Postpartum visit and care transition. ACOG recommends a comprehensive postpartum visit at 4 to 12 weeks to fully evaluate the woman's physical, social, and psychologic well-being and to serve as a transition from pregnancy care to well-woman care. This is a large order and includes evaluation of the following:

- mood and emotional well-being
- infant care and feeding
- sexuality, contraception, and birth spacing
- sleep and fatigue
- physical recovery from birth
- chronic disease management and transition to primary care provider
- health maintenance
- review of labor and delivery course if needed
- review of risks and recommendations for future pregnancies.

After these components are addressed, it is expected that the patient will be transitioned to a primary care provider (who may continue to be the ObGyn, as appropriate) to coordinate her future care in the primary medical home.

Useful resource for adopting new paradigm

ACOG's recommendations are somewhat daunting, and these changes will require education and resources, a significant increase in obstetric provider time and effort, and consideration of policy change regarding such issues as parental leave and postpartum care reimbursement. As a start, ACOG has developed an online aid for health care providers called "Postpartum toolkit" (https://www.acog.org/About-ACOG/ACOG-Departments/Toolkits-for-Health-Care-Providers/Postpartum-Toolkit), which provides education and resources for all steps in the process and can be individualized for each practice and patient.[7]

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Challenges in managing chronic pelvic pain in women

At the 2018 Pelvic Anatomy and Gynecologic Surgery Symposium, held in Las Vegas, Nevada (December 6 to 8), Tommaso Falcone, MD, and Mickey Karram, MD, co-chaired a dynamic meeting. Topics ranged from facilitating vaginal procedures safely and effectively to surgery for stress incontinence and pelvic organ prolapse and safe use of energy devices and endometriosis management. A keynote lecture featured Sawsan As-Sanie, MD, MPH, on chronic pelvic pain management.

John Baranowski, Contributing Editor

Medical science's broad knowledge of endometriosis notwithstanding, "many questions remain unanswered" about the management of a condition that is often refractory to established therapies, observed Dr. As-Sanie, who is Associate Professor and Director, Minimally Invasive Gynecologic Surgery Fellowship, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor. How, then, should clinicians approach the challenge of caring for women with this enigmatic disease in the larger context of chronic pelvic pain (CPP), in which, as Dr. As-Sanie said, "one size never fits all"?

Complex correlation between endometriosis and CPP

Despite high prevalence and negative impact on the health and quality of life of women who have endometriosis, Dr. As-Sanie emphasized, it remains unclear why only some women with endometriosis develop CPP and why there is little, if any, correlation between disease severity and the intensity of pain.

The clinical approach to endometriosis and CPP can be frustrating for several reasons: there is minimal relationship between extent or location of disease with pain symptoms; there is no consistent relationship among inflammatory markers, nerve-fiber density, and pain symptoms; and pain can recur *after* medical and surgical therapy—often without evidence of recurrent endometriosis. Furthermore, the differential diagnosis of CPP is broad, and also includes adenomyosis, adhesions, chronic pelvic inflammatory disease, uterine fibroids, pelvic congestion, ovarian remnant, and residual ovarian syndrome. Chronic overlapping pain conditions are prevalent, too, including interstitial cystitis, irritable bowel syndrome, and vulvodynia, to name a few.[1]

CPP is not just a pain disorder

Dr. As-Sanie said that understanding of CPP must extend to include fatigue, memory difficulties, poor sleep, and heightened sensitivity to multiple sensory stimuli (eg, sound and light).[2] So what, she asked, do we know about endometriosis, chronic pelvic pain, and the brain? We know that CPP, with and without

FAST TRACK

CPP, with and without endometriosis, is associated with increased pain sensitivity and altered central nervous system structure and function

endometriosis, is associated with increased pain sensitivity and altered central nervous system structure and function.[3-5] Central amplification of pain can lead to chronic pain independent of nociceptive signals, including multifocal, widespread pain; higher lifetime history of pain throughout the body; and pain triggered or exacerbated by stressors. And CPP brings with it other, potentially debilitating problems, including elevated distress, decreased activity, isolation, poor sleep, and maladaptive illness behaviors.

Finding, then addressing, the culprit

Identifying the underlying cause(s) of CPP in the individual woman should guide clinical care. This includes the decision to proceed with, or avoid, surgery. Remember: Patients with centralized pain respond differently to therapy; surgery is less likely to help relieve the pain.

Dr. As-Sanie offered several fundamental guidelines for managing CPP:

- Treat early, to prevent transition from acute to chronic pain; treatment delay increases connectivity between pain regulatory regions.
- Hysterectomy is not definitive therapy for all women with endometriosis or CPP.[6]
- Take a multisystem approach, comprising medical, behavioral, and interventional strategies.
- If an organ- or disease-based diagnostic and treatment approach does not work, reconsider the diagnosis; re-evaluate comorbid psychosocial variables; and consider treating centralized pain.
- Choice of treatment should include consideration of cost and adverse-effect profile.
- If one modality is ineffective, try another.

FAST TRACK

For centralized pain treatment, evidence is strong for dual reuptake-inhibitor antidepressants and anti-convulsants with analgesic properties

What are the levels of evidence for centralized pain treatment?

Available pharmacotherapeutic agents have modest benefit, possibly because the population of pain patients is heterogeneous, with various underlying mechanisms of pain. And, Dr. As-Sanie pointed out, clinical tools do not currently exist to pre-emptively select the right medicine for individual patients.

Evidence is strong, Dr. As-Sanie noted, for dual reuptake-inhibitor antidepressants, such as tricyclic compounds (amitriptyline, cyclobenzaprine) and serotonin–norepinephrine reuptake inhibitors, and for anticonvulsants with analgesic properties (pregabalin, gabapentin). Evidence is "modest," Dr. As-Sanie said, for tramadol, gamma hydroxybutyrate, and low-dose naltrexone, and "weak" for cannabinoids, human growth hormone, 5-hydroxytryptamine, tropisetron, and S-adenosyl-L-methionine. There is *no* evidence for using opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and non–benzodiazepine hypnotics, or guaifenesin.[7]

When surgery or pharmacotherapy alone fail to yield the necessary outcome, consider adjunctive nonpharmacotherapy.[8] For example, there is strong evidence for patient education, aerobic exercise, and cognitive-behavioral therapy; modest evidence for acupressure, acupuncture, strength training, hypnotherapy, biofeedback, trigger-point injection, and neuromodulation; but only weak evidence for chiropractic, manual and massage therapy, electrotherapy, and ultrasound.[7]

With CPP, "one size never fits all"

Dr. As-Sanie concluded with a reminder that CPP can be the product of any of a range of underlying contributory causes. Pathology might stand foremost as you search for the source of pain and an effective treatment, but keep in mind that genetics, environment, coexisting pain conditions, the patient's ability to cope, and her resilience and social support might play a role. ●

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The Medical Intelligence Quiz

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Addressing your patient's sexual function after cancer

Stacy Tessler Lindau, MD
Professor of Obstetrics/Gynecology and Medicine-Geriatrics; Director of the Program in Integrative Sexual Medicine and WomanLab
University of Chicago Medicine, Chicago, Illinois

Women undergoing a cancer diagnosis and management plan want their physicians to raise the issue of sexual function, says Dr. Lindau. And oncologists may refer patients to you specifically for help with addressing those needs. Dr. Lindau addresses what ObGyns should know about sex and cancer, focusing in on improving female sexual function outcomes in the cancer setting, both before and after treatment, and the need to validate patients' concerns about sexual function when raised.

The opioid crisis: Treating pregnant women with addiction

Mishka Terplan, MD, MPH
Professor, Obstetrics and Gynecology and Psychiatry; Associate Director, Addiction Medicine
Virginia Commonwealth University, Richmond, Virginia

Dr. Terplan discusses why women are "the face of the opioid epidemic" and presents clinical pearls for managing the treatment of pregnant women with addiction.

Maternal immunization: What does the future hold?

Kevin Ault, MD
Professor and Division Director, General Obstetrics and Gynecology
University of Kansas School of Medicine, Kansas City

Dr. Ault relays the past, present, and future of maternal immunization.

Which IUD is right for me? Answering your patients' questions about differences in LNG-IUDs

Juliana Melo, MD, MSCS, and Melissa Chen, MD, MPH
Drs. Melo and Chen are Assistant Professors, Obstetrics and Gynecology
University of California, Davis

In this audiocast, Drs. Melo and Chen compare the 3 different types of levonorgestrel-releasing intrauterine devices and discuss how to choose an IUD for each patient. They also review side effects, including insertion pain and expulsion, and extended use options.

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PRODUCT Update

PREIMPLANTATION GENETIC TESTING

Spectrum® preimplantation genetic screening for aneuploidy (PGT-A) from **Natera, Inc**, has demonstrated that it improves in vitro fertilization (IVF) results for all women, including those of advanced maternal age, announces **Natera**.

In a retrospective study published in *Fertility and Sterility,* **Spectrum**, a single-nucleotide polymorphism (SNP)-based PGT-A technology, was successful in screening all 24 chromosomes to provide comprehensive embryo aneuploidy results. **Natera** says that the study results showed that use of **Spectrum** PGT-A during IVF led to excellent implantation (70%), clinical pregnancy (71%), and live birth (65%) rates during single embryo transfer.

Spectrum evaluates the number of chromosomes in embryos to detect extra or missing chromosomes and screens for inherited genetic disorders to help provide the best chance of transferring a healthy embryo with the correct number of chromosomes.

FOR MORE INFORMATION, VISIT:
https://www.natera.com/spectrum

PORTABLE BREAST ULTRASOUND

The **Viera™ Portable Breast Ultrasound System** from **Hologic** is now available for purchase in the United States.

Viera is a wireless, handheld breast ultrasound scanner that **Hologic** says produces exceptional image quality. The scanner uses a 14-4 MHz linear transducer, contains 192 elements, and has 4 parallel software beamformers. It utilizes spatial compounding to reduce image noise and speckle. Presets are available for breast, dense breast, and interventional procedures with B, M, power Doppler, color Doppler, and needle enhancement modes. On-demand high-resolution images are transmitted wirelessly to smart devices and patient archive systems (PACS) in the office, exam room, or surgical suite, or to the Cloud for efficient documentation. Smart device platforms include iOS and Android devices using WiFi and Bluetooth connectivity. The system includes a 1.2-lb scanner, 2 rechargeable batteries, and a charger with global AC adapter.

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

HOME SPERM TEST

The **YO Home Sperm Test**, which allows a man to test his moving sperm in private, is the first test of its kind to receive FDA approval, announces **Medical Electronic Systems** (MES). A soon-to-be-published study shows **YO** to be highly accurate, says **MES**. Offering automated sperm analyzers to hospital labs, universities, and IVF centers, **MES** adapted its technology to a home setting after realizing that many men are hesitant to be tested in a clinical venue.

The customer downloads the smart-phone app and acquires the **YO Kit**. After collecting a semen sample, he uses a pipette from the kit to place semen on a slide, which is slipped into the Yo Clip. The clip slides onto the smartphone, which uses its camera to take a high-resolution video. Test results and the sperm video appear in about 2 minutes.

At $59.95, the **YO Kit** includes 2 tests, in case a second sample is desired.

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

IMPROVING THE MAMMOGRAPHY EXPERIENCE

Fear of pain during mammography is a major reason why women avoid screening, says **Hologic**, who designed the **SmartCurve™ Breast Stabilization System** to provide a better patient experience. With a curved design that mirrors a woman's breast, the system has been clinically proven to deliver a more comfortable mammogram. **SmartCurve** has been shown to improve comfort in 93% of patients who reported moderate to severe discomfort with standard compression technology. The curved design reduces pinching while allowing uniform compression over the entire breast. Specialized processing software takes the geometry of the curved surface into account, so that resulting images have the same appearance as images taken with standard equipment.

SmartCurve is standard on **Hologic**'s new **3Dimensions™** mammography system and as an enhancement option to existing **Hologic Selenia® Dimensions®** systems.

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

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348 women in late postmenopause (median age, 63.6 years).

For women in the estradiol-treated group, mean E2 levels during the trial as well as change of E2 levels from baseline were significantly higher in the early postmenopause group than in the late postmenopause group, even though both groups had similar adherence based on pill count. For those in the placebo group, mean E2 levels and change of E2 levels from baseline were equivalent in early and late menopause.

In the E2-treated group and the placebo group combined, the mixed effects analysis of the CIMT progression rate (based on the mean E2 level during the trial) demonstrated that a higher level of E2 was inversely associated with the CIMT progression rate in early postmenopausal women (beta coefficient = -0.04 [95% confidence interval (CI), -0.09 to -0.001] µm CIMT per year per 1 pg/mL estradiol; P = .04). However, a higher level of E2 was positively associated (beta coefficient = 0.063 [95% CI, 0.018 to 0.107] µm CIMT per year per 1 pg/mL estradiol; P = .006) with CIMT progression rate in the late postmenopausal women.

Bottom line. E2 levels resulting from administration of oral estradiol were inversely associated with atherosclerosis progression in women in early menopause, but they were positively associated with progression in late postmenopause participants. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

These new findings from a posttrial analysis of ELITE data provide yet further support for the hormone therapy (HT) "timing hypothesis," which postulates that HT slows atherosclerosis progression in recently menopausal women but has neutral or adverse effects in women who are at least a decade past menopause onset. As the authors suggest, the favorable vascular effects of E2 appear limited to those women (most often in early menopause) who have not yet developed atherosclerosis. Whether or not HT should be considered for cardioprotection remains unresolved (and controversial). By contrast, these data, along with findings from the Women's Health Initiative,[3] provide reassurance regarding the cardiovascular safety of HT when prescribed for recently menopausal women with bothersome vasomotor symptoms.

ANDREW M. KAUNITZ, MD

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How does HT in recent and 10+ years past menopause affect atherosclerosis progression?

Secondary analysis of ELITE trial data among 596 women in early (<6 years) and late (≥10 years) postmenopause indicates that **estradiol (E2) plasma levels** resulting from oral E2 administration were **inversely associated with atherosclerosis progression in the women in early menopause, but positively associated with atherosclerosis progression in those in late menopause**

FAST TRACK

While E2 administration was inversely associated with atherosclerosis progression in women in early menopause, it was positively associated with atherosclerosis progression in women in late menopause

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

Sriprasert I, Hodis HN, Karim R, et al. Differential effect of plasma estradiol on subclinical atherosclerosis progression in early versus late postmenopause. J Clin Endocrinol Metab. 2019;104:293-300. doi:10.1210/jc.2018-01600.

In 2016, the primary findings of the Early versus Late Intervention Trial with Estradiol (ELITE) demonstrated that oral E2 administered to women who were less than 6 years postmenopause slowed progression of subclinical atherosclerosis as assessed by carotid artery intima-media thickness (CIMT), while it had no effect in women who were at least 10 years postmenopause.[1]

That trial included 643 healthy women without cardiovascular disease who at enrollment had a median age of 55.4 years in the early postmenopause group (median 3.5 years since menopause) and 63.6 years in the late postmenopause group (median 14.3 years since menopause). The study medications were oral estradiol 1 mg daily plus progesterone vaginal gel for women with a uterus or placebo and placebo gel for a median of 5 years.

The investigators found also that, in contrast with CIMT, cardiac computed tomography (CT) measures of atherosclerosis did not differ significantly between the estradiol and placebo groups, regardless of age.[1]

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

Posttrial data analysis revealed a new finding

In a secondary analysis of data from the ELITE trial, Sriprasert and colleagues dug deeper to assess the impact of plasma E2 levels on progression of subclinical atherosclerosis.[2]

Among 596 women (69.6% white non-Hispanic, 8.7% black, 13.3% Hispanic, and 8.4% Asian/Pacific Islander), E2 levels were available in 248 women in early postmenopause (mean age, 54.7 years) and

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BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
ParaGard® T 380A Intrauterine Copper Contraceptive

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ParaGard® is indicated for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies has been less than 1 pregnancy per 100 women each year.

CONTRAINDICATIONS

ParaGard® should not be placed when one or more of the following conditions exist:

1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease, or current behavior suggesting a high risk for pelvic inflammatory disease
4. Postpartum endometritis or postabortal endometritis in the past 3 months
5. Known or suspected uterine or cervical malignancy
6. Genital bleeding of unknown etiology
7. Mucopurulent cervicitis
8. Wilson's disease
9. Allergy to any component of ParaGard®
10. A previously placed IUD that has not been removed

WARNINGS

1. Intrauterine Pregnancy

If intrauterine pregnancy occurs with ParaGard® in place and the string is visible, ParaGard® should be removed because of the risk of spontaneous abortion, premature delivery, sepsis, septic shock, and, rarely, death. Removal may be followed by pregnancy loss.

If the string is not visible, and the woman decides to continue her pregnancy, check if the ParaGard® is in her uterus (for example, by ultrasound). If ParaGard® is in her uterus, warn her that there is an increased risk of spontaneous abortion and sepsis, septic shock, and rarely, death. In addition, the risk of premature labor and delivery is increased.

Human data about risk of birth defects from copper exposure are limited. However, studies have not detected a pattern of abnormalities, and published reports do not suggest a risk that is higher than the baseline risk for birth defects.

2. Ectopic Pregnancy

Women who become pregnant while using ParaGard® should be evaluated for ectopic pregnancy. A pregnancy that occurs with ParaGard® in place is more likely to be ectopic than a pregnancy in the general population. However, because ParaGard® prevents most pregnancies, women who use ParaGard® have a lower risk of an ectopic pregnancy than sexually active women who do not use any contraception.

3. Pelvic Infection

Although pelvic inflammatory disease (PID) in women using IUDs is uncommon, IUDs may be associated with an increased relative risk of PID compared to other forms of contraception and to no contraception. The highest incidence of PID occurs within 20 days following insertion. Therefore, the visit following the first post-insertion menstrual period is an opportunity to assess the patient for infection, as well as to check that the IUD is in place. Since pelvic infection is most frequently associated with sexually transmitted organisms, IUDs are not recommended for women at high risk for sexual infection. Prophylactic antibiotics at the time of insertion do not appear to lower the incidence of PID.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID. Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

The significance of actinomyces-like organisms on Papanicolaou smear in an asymptomatic IUD user is unknown, and so this finding alone does not always require IUD removal and treatment. However, because pelvic actinomycosis is a serious infection, a woman who has *symptoms* of pelvic infection possibly due to actinomyces should be treated and have her IUD removed.

4. Immunocompromise

Women with AIDS should not have IUDs inserted unless they are clinically stable on antiretroviral therapy. Limited data suggest that asymptomatic women infected with human immunodeficiency virus may use intrauterine devices. Little is known about the use of IUDs in women who have illnesses causing serious immunocompromise. Therefore these women should be carefully monitored for infection if they choose to use an IUD. The risk of pregnancy should be weighed against the theoretical risk of infection.

5. Embedment

Partial penetration or embedment of ParaGard® in the myometrium can make removal difficult. In some cases, surgical removal may be necessary.

6. Perforation

Partial or total perforation of the uterine wall or cervix may occur rarely during placement, although it may not be detected until later. Spontaneous migration has also been reported. If perforation does occur, remove ParaGard® promptly, since the copper can lead to intraperitoneal adhesions. Intestinal penetration, intestinal obstruction, and/or damage to adjacent organs may result if an IUD is left in the peritoneal cavity. Pre-operative imaging followed by laparoscopy or laparotomy is often required to remove an IUD from the peritoneal cavity.

7. Expulsion

Expulsion can occur, usually during the menses and usually in the first few months after insertion. There is an increased risk of expulsion in the nulliparous patient. If unnoticed, an unintended pregnancy could occur.

8. Wilson's Disease

Theoretically, ParaGard® can exacerbate Wilson's disease, a rare genetic disease affecting copper excretion.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Information for patients

Before inserting ParaGard® discuss the Patient Package Insert with the patient, and give her time to read the information. Discuss any questions she may have concerning ParaGard® as well as other methods of contraception. Instruct her to promptly report symptoms of infection, pregnancy, or missing strings.

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

In the 2 largest clinical trials with ParaGard®, menstrual changes were the most common medical reason for discontinuation of ParaGard®. Discontinuation rates for pain and bleeding combined are highest in the first year of use and diminish thereafter. The percentage of women who discontinued ParaGard® because of bleeding problems or pain during these studies ranged from 11.9% in the first year to 2.2 % in year 9. Women complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue ParaGard®.

4. Vasovagal reactions, including fainting

Some women have vasovagal reactions immediately after insertion. Hence, patients should remain supine until feeling well and should be cautious when getting up.

5. Expulsion following placement after a birth or abortion

ParaGard® has been placed immediately after delivery, although risk of expulsion may be higher than when ParaGard® is placed at times unrelated to delivery. However, unless done immediately postpartum, insertion should be delayed to the second postpartum month because insertion during the first postpartum month (except for immediately after delivery) has been associated with increased risk of perforation.

ParaGard® can be placed immediately after abortion, although immediate placement has a slightly higher risk of expulsion than placement at other times. Placement after second trimester abortion is associated with a higher risk of expulsion than placement after the first trimester abortion.

6. Magnetic resonance imaging (MRI)

Limited data suggest that MRI at the level of 1.5 Tesla is acceptable in women using ParaGard®. One study examined the effect of MRI on the CU-7® Intrauterine Copper Contraceptive and Lippes Loop™ intrauterine devices. Neither device moved under the influence of the magnetic field or heated during the spin-echo sequences usually employed for pelvic imaging. An in vitro study did not detect movement or temperature change when ParaGard® was subjected to MRI.

7. Medical diathermy

Theoretically, medical (non-surgical) diathermy (short-wave and microwave heat therapy) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. However, a small study of eight women did not detect a significant elevation of intrauterine temperature when diathermy was performed in the presence of a copper IUD.

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

Nursing mothers may use ParaGard®. No difference has been detected in concentration of copper in human milk before and after insertion of copper IUDs. The literature is conflicting, but limited data suggest that there may be an increased risk of perforation and expulsion if a woman is lactating.

10. Pediatric use

ParaGard® is not indicated before menarche. Safety and efficacy have been established in women over 16 years old.

ADVERSE REACTIONS

The most serious adverse events associated with intrauterine contraception are discussed in **WARNINGS** and **PRECAUTIONS**. These include:

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

The following adverse events have also been observed. These are listed alphabetically and not by order of frequency or severity.

Anemia	Menstrual flow, prolonged
Backache	Menstrual spotting
Dysmenorrhea	Pain and cramping
Dyspareunia	Urticarial allergic skin reaction
Expulsion, complete or partial	Vaginitis
Leukorrhea	

CooperSurgical

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This brief summary is based on the ParaGard full prescribing information dated September 2014.

PAR-41287 01/18

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Satisfy more patients with Paragard—the only highly effective, reversible birth control that is completely hormone free. Learn more at **hcp.paragard.com** or call **1-877-PARAGARD**.

Indication

Paragard is intended for intrauterine contraception for up to 10 years.

Important Safety Information

- Paragard must not be used by women who have acute pelvic inflammatory disease (PID); have had a postpregnancy or postabortion uterine infection in the past 3 months; have cancer of the uterus or cervix; have an infection of the cervix; have an allergy to any component; or have Wilson's disease.
- If a woman misses her period, she must be promptly evaluated for pregnancy.
- Possible serious complications that have been associated with intrauterine contraceptives are PID, embedment, perforation of the uterus, and expulsion.
- Paragard must not be used by women who are pregnant as this can be life threatening and may result in loss of pregnancy or infertility.
- The most common side effects of Paragard are bleeding and spotting; for most women, these typically subside after 2 to 3 months.
- **Paragard does not protect against HIV or other sexually transmitted infections (STI).**

Please see the following page for a brief summary of full Prescribing Information.

Over 6 million Paragard units distributed[3]

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intrauterine copper contraceptive
simple, honest pregnancy prevention™

CooperSurgical

References: 1. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use; 2017. **2.** Kaneshiro B, Aeby T. Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010;2:211-220. **3.** Data on file, March 2018. CooperSurgical, Inc.

*According to the Centers for Disease Control and Prevention (CDC), Paragard is one of the least restrictive birth control options across all patient types compared to other IUDs.