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OBG MANAGEMENT

30th ANNIVERSARY

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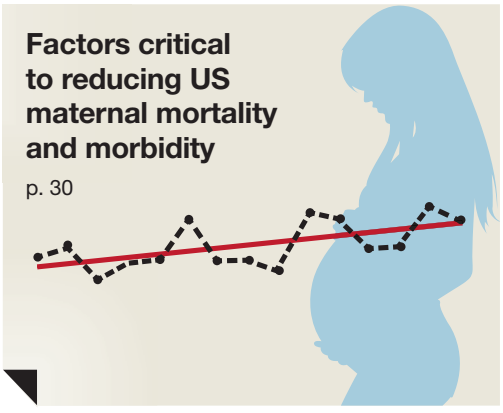

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NEXPLANON is indicated for use by women to prevent pregnancy.

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.

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WOMN-1233494-0000 10/17

NEXPLANON — 1 ARM IMPLANT provides up to 3 years of pregnancy prevention*

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

(Actual implant shown;
actual implant size is 4cm)

>99% effective†

Placed subdermally in the inner upper arm just under the skin

***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.

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.

Nexplanon®
(etonogestrel implant) 68mg

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 increase breakthrough bleeding.

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

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

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.

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MERCK

#1 IN READERSHIP!*

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

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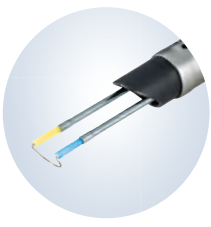

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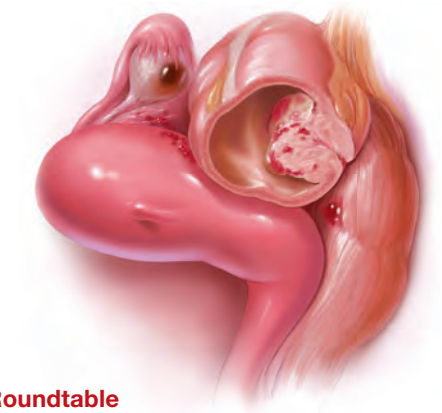

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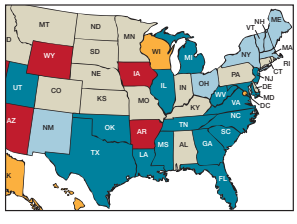

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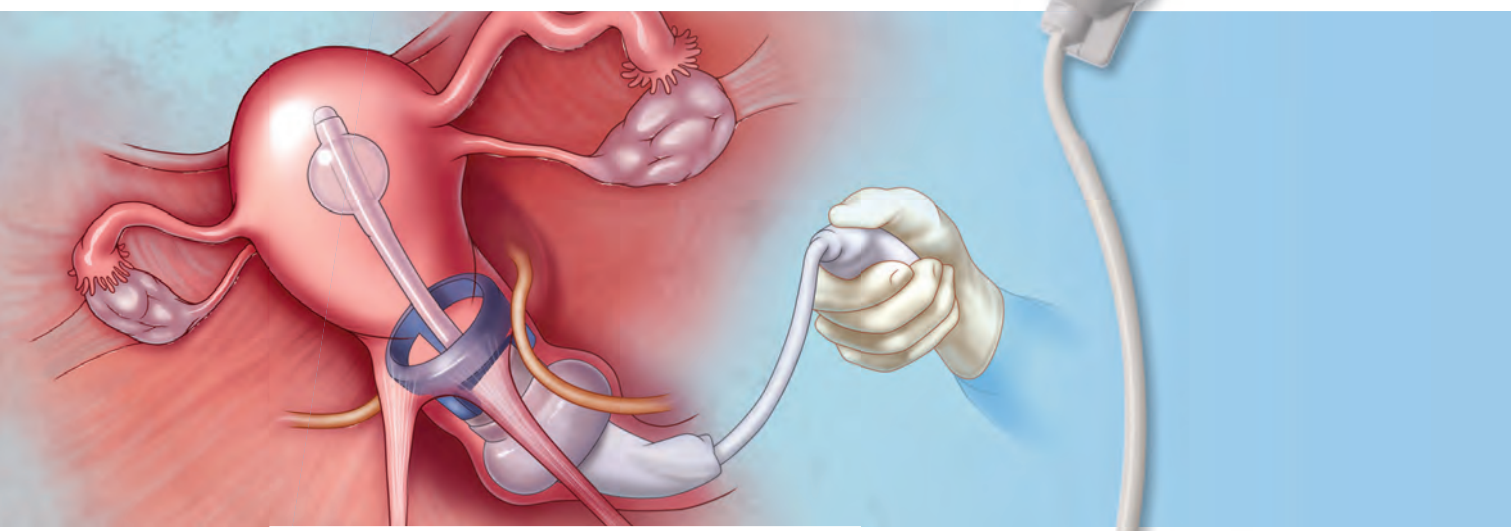

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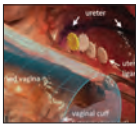

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Hidradenitis suppurativa: An underdiagnosed skin problem of women

Gynecologists are uniquely positioned to diagnose this common skin problem

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In recent decades the practice of medicine has drifted away from the performance of a physical examination during most patient encounters and evolved toward the more intensive use of history, imaging, and laboratory studies to guide management decisions. For example, it is common for a woman to present to an emergency department with abdominal or pelvic pain and undergo a computerized tomography scan before an abdominal and pelvic examination is performed. Some authorities believe that the trend to reduce the importance of the physical examination has gone way too far and resulted in a reduction in the quality of health care.[1,2]

Many skin diseases only can be diagnosed by having the patient disrobe and examining the skin. Gynecologists are uniquely positioned to diagnose important skin diseases because, while performing a reproductive health examination, they may be the first clinicians to directly examine the anogenital area and inner thighs. Skin diseases that are prevalent and can be diagnosed while performing an examination of the anogenital region include lichen sclerosus (LS) and hidradenitis suppurativa (HS). The prevalence of each of these conditions is in the range of 1% to 4% of women.[3–5]

Failure to examine the anogenital area and insufficient attention to the early signs of LS and HS may result in a long delay in the diagnosis.[6] In 1 survey, of 517 patients with HS, there was a 7-year interval between the onset of the disease and the diagnosis by a clinician.[7] Delay in diagnosis results in increased scarring, which makes it more difficult to effectively treat the disease. In this editorial, I will focus on the pathogenesis, diagnosis, and treatment of HS.

Diagnosis, presentation, and staging

Hidradenitis suppurativa (from the Greek, hidros means sweat and aden means glands) is a painful, chronic, relapsing, inflammatory skin disorder affecting the follicular unit. It is manifested by nodules, pustules, sinus tracts, and scars, usually in intertriginous areas. The diagnosis is made by history and physical examination. The 3 cardinal features of HS are 1) deep-seated nodules, comedones, and fibrosis; 2) typical anatomic location of the lesions in the axillae, inguinocrural, and anogenital regions, and 3) chronic relapsing course.[8]

Disease severity is often assessed using the Hurley staging system:

- stage I: abscess formation without sinus tracts or scarring (**FIGURE**, page 10)
- stage II: recurrent abscesses with tract formation and scarring, widely separated lesions

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Instant Poll

Do you think that the trend to not perform a physical examination has adversely impacted patient care? Without violating HIPAA provisions, are you aware of a case example of how not performing a physical examination adversely impacted patient care?

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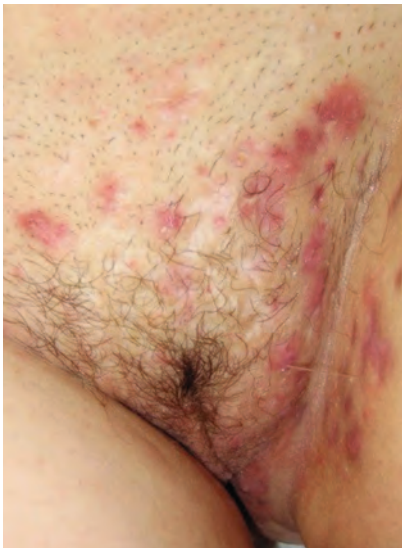

FIGURE Multiple inflammatory nodules in the genital area without sinus tracts or fistulas, classified as Hurley stage I disease.

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- stage III: diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses.

In one report, stage I, II, and III disease was diagnosed in 65%, 31%, and 4% of cases, respectively, indicating that most HS is diagnosed in stage I and suitable for treatment by a gynecologist.[9]

HS typically presents after puberty and women are more commonly affected than men. In one case series including 232 women with HS the regions most commonly affected were: axillae, inguinofemoral, urogenital, and buttocks in 79%, 77%, 51%, and 40% of cases, respectively.[10] Risk factors for HS include obesity, cigarette smoking, tight fitting clothing, and chronic friction across the affected skin area.[5]

Pathogenesis

The pathophysiology of HS is thought to begin with occlusion of the follicle, resulting in follicle rupture deep in the dermis, thereby triggering inflammation, bacterial infection, and scarring. Dermal areas affected by HS have high concentrations of cytokines, including tumor necrosis factor (TNF)–alpha, interleukin (IL)-1-beta, IL-23, and IL-32.[11,12] Once HS becomes an established process, it is difficult to treat because the dermal inflammatory process and scarring provides a microenvironment that facilitates disease progression. Hence early detection and treatment may result in optimal long-term outcomes.

Treatment

Many recommended treatments for HS have not been formally tested in large randomized trials. A recent Cochrane review identified only 12 high-quality trials and the median number of participants was 27 per trial.[13] Consequently, most treatment recommendations are based on expert opinion. Recommended treatments include smoking cessation, weight loss, topical and systemic antibiotics, antiandrogens, anti-inflammatory biologics (adalimumab and infliximab), and surgery. Smoking cessation and weight loss are strongly recommended in the initial treatment of HS. Bariatric surgery and significant postprocedure weight loss has been reported to cause a reduction in disease activity.[14]

Stage I management. For the initial treatment of stage I HS, **clindamycin gel 1%** applied twice daily to affected areas is recommended.[15] Recommended oral antibiotic treatments include **tetracycline 500 mg twice daily for 12 weeks**[16] or **doxycycline 100 mg or 200 mg given daily for 10 weeks** or **clindamycin 300 mg twice daily plus rifampicin 600 mg once daily for 10 weeks.**[17,18] These antibiotics have both antimicrobial and anti-inflammatory effects.

Hormonal interventions that suppress androgen production or action may help reduce HS disease activity. For women with HS who also need contraception, an **estrogen-progestin contraceptive** may help reduce HS disease activity in up to 50% of individuals.[19] The 5-alpha reductase inhibitor finasteride, at high doses (5 to 15 mg daily), has been reported to reduce HS disease activity.[20,21] Finasteride is a teratogen, and the FDA strongly recommends against its use by women. Spironolactone, an antimineralocorticoid and antiandrogen, at a dose of 100 mg daily has been reported to reduce disease activity in about 50% of treated individuals and is FDA approved for use in women.[22] Among reproductive-age women, spironolactone, which is a teratogen, only should be prescribed to women using an effective form of contraceptive. HS is often associated with obesity and insulin resistance. Metformin 500 mg three times daily has been reported to decrease disease activity.[23,24]

Stage II or III management. For Hurley stage II or III HS, referral to a dermatologist is warranted. There is evidence that too few people with HS are referred to a dermatologist.[25] For severe HS resistant to oral medications, anti-TNF monoclonal antibody treatment with **adalimumab** (Humira) or **infliximab** (Remicade) is effective. Adalimumab is administered by subcutaneous injection and is US Food and Drug Administration (FDA)–approved to treat HS. Following a loading dose, adalimumab is administered weekly at a dose of 40 mg.[26] Infliximab, which is not FDA approved to treat HS, is administered by intravenous infusion at a dose of 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks.[27]

Surgical management. HS is sometimes treated surgically with

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laser destruction of lesions, punch debridement, or wide excision of diseased tissue.[28,29] There are no high quality clinical trials of surgical treatment of HS. Punch debridement can be performed using a 5- to 7-mm circular skin punch to deeply excise the inflamed follicle. Wide excision can be followed by wound closure with advancement flaps or split-thickness skin grafting. Wound closure by secondary intention is possible but requires many weeks or months of burdensome dressing changes to complete the healing process. Recurrence is common following surgical therapy and ranges from 30% with deroofing or laser treatment to 6% following wide excision and skin graft closure of the wound.[30]

Physical examination vital to early diagnosis

Delay in diagnosis of an active disease process has many causes, including nonperformance of a physical examination. In a web-based survey of physicians' experiences with oversights related to the physical examination, 3 problems frequently reported were: nonperformance of any portion of the physical examination, failure to undress the patient to examine the skin, and failure to examine the abdomen and anogenital region in a patient with abdominal or pelvic pain.[31] Oversights in the physical examination frequently caused a delay in diagnosis and treatment. With both LS and HS, patients may not recognize that they have a skin disease, or they may be embarrassed to show a clinician a skin change they have noticed. Early diagnosis and treatment are essential to achieving a good outcome and make a tremendous difference in the quality of life for the patient. Physical examination is a skill we have learned through diligent study and experience in practice. We can use these skills to greatly improve the lives of our patients. ●

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RECOGNIZE AND TREAT IRON DEFICIENCY ANEMIA IN PREGNANT WOMEN

JULIANNA SCHANTZ-DUNN, MD, MPH, AND ROBERT L. BARBIERI, MD (EDITORIAL; DECEMBER 2017)

Consider thalassemia traits in patients with iron deficiency

The editorial is an excellent review of iron deficiency as an associated finding with adverse health and pregnancy outcomes. However, one genetic issue appears to have escaped comment. In Florida, our African American patients have a commonly found association with microcytic anemia at least as often as iron deficiency: a variety of α- and ß-thalassemia traits that may occur individually or together. Other racial groups, including Mediterranean and Asian patients, also may carry both the α- and ß-thalassemia traits.

Your recommendation to routinely screen for ferritin deficit is laudable as a general health care practice. If the screening result is normal, however, consider thalassemia carrier states as a secondary explanation as well as a genetic issue requiring partner testing. Aggressive iron loading of a nondeficient anemic patient can risk excess absorption, storage, and ultimate organ compromise in later life if continued indefinitely.

Richard P. Perkins, MD
Fort Myers, Florida

Patient education is key to managing iron deficiency

Forty years ago, my professors expounded on how some people could not absorb iron and that the answer was intravenous iron infusion. After writing a few prescriptions, however, I found that I no longer had patients with absorptive problems once I learned to carefully, and with visual aids, explain the iron story and

DECEMBER 2017

meticulously monitor compliance. I have been through the "slow Fe" and the "prenatal vitamins have iron" nonsense. Ferrous sulfate is about as good as anything. I have explained the theory of vitamin C–assist and found that telling people to avoid taking iron with meals is folly.

I suggest that the iron story is complete. Rather than wasting money on further research, we should spend funds on teaching young physicians to educate patients and monitor compliance. In recent years, I have found that a daily text message to the patient frequently is very helpful.

Robert W. Jackson, MD
Washougal, Washington

Dr. Barbieri responds

I thank Drs. Perkins and Jackson for their helpful recommendations for the management of iron deficiency anemia. I agree with Dr. Perkins that screening for thalassemia is an important part of preconception and prenatal care. In the editorial's table on page 10 discussing the differential diagnosis of anemia, we mentioned the importance of hemoglobin electrophoresis and measurement of vitamin B12 and folate levels to identify cases of anemia caused by thalassemia or vitamin deficiency. I agree with Dr. Jackson that oral iron supplementation along with patient education can resolve most cases of iron deficiency in early and mid-pregnancy. However, in the last few weeks of pregnancy there may not be sufficient time for oral iron supplementation to be effective in resolving iron deficiency anemia. In this situation and in patients at high risk for malabsorption, including women with prior gastric bypass, intravenous iron might be the best approach to resolving the anemia.

STOP USING CODEINE, OXYCODONE, HYDROCODONE, TRAMADOL, AND ASPIRIN IN WOMEN WHO ARE BREASTFEEDING

ROBERT L. BARBIERI, MD (EDITORIAL; OCTOBER 2017)

An either/or choice is not a good strategy for pain

I found Dr. Barbieri's editorial on postpartum opioid use and breastfeeding interesting, but one key issue was not addressed: Following this guidance means that new mothers have to choose between breastfeeding and pain control. You may explain to a patient with 2-day cesarean delivery pain, "If you take pain medicine while breastfeeding, it can adversely affect the baby. So we will give you acetaminophen." While some moms will deal with it, others will stop breastfeeding. With the increasing pressure to advocate for breastfeeding, this strategy is likely not realistic.

R. Lee Toler, DO
Bolivia, North Carolina

My pain management protocol

While presently in an office-based setting, back in my inpatient practice

CONTINUED ON PAGE 52

Which antibiotics should be used with caution in pregnant women with UTI?

Nitrofurantoin and trimethoprim-sulfamethoxazole have study data indicating their teratogenicity, and ACOG has recommended against use of these 2 agents in the first trimester of pregnancy unless other antibiotics are unlikely to be effective. Despite this recommendation, a recent large commercial database study indicated that 43% of women were prescribed nitrofurantoin or trimethoprim-sulfamethoxazole in their first trimester. These agents should be used with caution during the early part of pregnancy.

FAST TRACK

One goal of treating bacteriuria and cystitis is to prevent ascending infection (pyelonephritis); another is to use an antibiotic that eradicates the uropathogen without causing harm to the mother or fetus

Ailes EC, Summers AD, Tran EL, et al. Antibiotics dispensed to privately insured pregnant women with urinary tract infections—United States, 2014. MMWR Morb Mortal Wkly Rep. 2018;67(1):18–22.

EXPERT COMMENTARY

Patrick Duff, MD, is Associate Dean for Student Affairs and Professor of Obstetrics and Gynecology in the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville.

Lower urinary tract infection (UTI) is one of the most common medical complications of pregnancy. Approximately 5% to 10% of all pregnant women have asymptomatic bacteriuria, which usually antedates the pregnancy and is detected at the time of the first prenatal appointment. Another 2% to 3% develop acute cystitis during pregnancy. The dominant organisms that cause lower UTIs in pregnant women are *Escherichia coli, Klebsiella pneumoniae, Proteus* species, group B streptococci, enterococci, and *Staphylococcus saprophyticus*.

The author reports no financial relationships relevant to this article.

One goal of treating asymptomatic bacteriuria and acute cystitis is to prevent ascending infection (pyelonephritis), which can be associated with preterm delivery, sepsis, and adult respiratory distress syndrome. Another key goal is to use an antibiotic that eradicates the uropathogen without causing harm to either the mother or fetus.

In 2009, Crider and colleagues reported that 2 of the most commonly used antibiotics for UTIs, sulfonamides and nitrofurantoin, were associated with a disturbing spectrum of birth defects.[1] Following that report, in 2011 the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion that recommended against the use of these 2 agents in the first trimester of pregnancy unless other antibiotics were unlikely to be effective.[2]

Details of the study

Centers for Disease Control and Prevention investigators recently conducted a study to assess the effect of these ACOG recommendations on clinical practice. Ailes and coworkers used the Truven Health MarketScan

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Commercial Database to examine antibiotic prescriptions filled by pregnant women with UTIs.

The database included 482,917 pregnancies in 2014 eligible for analysis. A total of 7.2% (n = 34,864) of pregnant women were treated as outpatients for a UTI within the 90-day interval before the last menstrual period or during the pregnancy. Among these women, the most commonly prescribed antibiotics during the first trimester were nitrofurantoin (34.7%), ciprofloxacin (10.5%), cephalexin (10.3%), and trimethoprim-sulfamethoxazole (7.6%).

The authors concluded that 43% of women used an antibiotic (nitrofurantoin or trimethoprim-sulfamethoxazole) in the first trimester that had potential teratogenicity, despite the precautionary statement articulated in the ACOG committee opinion.[2]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Pending the publication of additional investigations, I believe that the guidance outlined below is prudent.

Trimethoprim-sulfamethoxazole should not be used for treating UTIs in the first trimester of pregnancy unless no other antibiotic is likely to be effective. This drug also should be avoided just prior to expected delivery because it can displace bilirubin from protein-binding sites in the newborn and increase the risk of neonatal jaundice.

There may be instances in which trimethoprim-sulfamethoxazole should be used even early in pregnancy, such as to provide prophylaxis against *Pneumocystis jiroveci* infection in women with human immunodeficiency virus.

To exercise an abundance of caution, I recommend that nitrofurantoin not be used in the first trimester of pregnancy unless no other antibiotic is likely to be effective.

Alternative antibiotics that might be used in the first trimester for treatment of UTIs include ampicillin, amoxicillin, cephalexin, and amoxicillin-clavulanic acid. Substantial evidence supports the safety of these antibiotics in early pregnancy. Unless no other drug is likely to be effective, I would not recommend use of a quinolone antibiotic, such as ciprofloxacin, because of concern about the possible injurious effect of these agents on cartilaginous tissue in the developing fetus.

Neither trimethoprim-sulfamethoxazole nor nitrofurantoin should be used at any time in pregnancy in a patient who has glucose-6-phosphate dehydrogenase deficiency or who may be at increased risk for this disorder.[2]

PATRICK DUFF, MD

Antibiotic-associated effects

Of all the antibiotics that could be used to treat a lower UTI in pregnancy, nitrofurantoin probably has the greatest appeal. The drug is highly concentrated in the urine and is very active against all the common uropathogens except *Proteus* species. It is not absorbed significantly outside the lower urinary tract, and thus it does not alter the natural flora of the bowel or vagina (such alteration would predispose the patient to antibiotic-associated diarrhea or vulvovaginal candidiasis). Nitrofurantoin is inexpensive and usually is very well tolerated.

In the National Birth Defects Prevention Study by Crider and colleagues, nitrofurantoin was associated with anophthalmia or microphthalmos (adjusted odds ratio [AOR], 3.7; 95% confidence interval [CI], 1.1–12.2), hypoplastic left heart syndrome (AOR, 4.2; 95% CI, 1.9–9.1), atrial septal defects (AOR, 1.9; 95% CI, 1.1–3.4), and cleft lip with cleft palate (AOR, 2.1; 95% CI, 1.2–3.9).[1] Other investigations, including one published as recently as 2013, have not documented these same associations.[3]

Similarly, the combination of trimethoprim-sulfamethoxazole also has considerable appeal for treating lower UTIs in pregnancy because it is highly active against most uropathogens, is inexpensive, and usually is very well tolerated. The report by Crider and colleagues, however, was even more worrisome with respect to the possible teratogenicity of this antibiotic.[1] The authors found that use of this antibiotic in the first trimester was associated with anencephaly (AOR, 3.4; 95% CI, 1.3–8.8), coarctation of the aorta (AOR, 2.7; 95% CI, 1.3–5.6), hypoplastic left heart (AOR, 3.2; 95% CI, 1.3–7.6), choanal atresia (AOR, 8.0; 95% CI, 2.7–23.5), transverse limb deficiency (AOR, 2.5; 95% CI, 1.0–5.9), and diaphragmatic hernia (AOR, 2.4; 95% CI, 1.1–5.4). Again, other authors, using different epidemiologic methods, have not found the same associations.[3]

Study strengths and weaknesses

The National Birth Defects Prevention Study by Crider and colleagues was a large,

well-funded, and well-designed epidemiologic study. It included more than 13,000 patients from 10 different states.

Nevertheless, the study had certain limitations.[4] The findings are subject to recall bias because the investigators questioned patients about antibiotic use *after*, rather than *during,* pregnancy. Understandably, the investigators were not able to verify the prescriptions for antibiotics by reviewing each individual medical record. In fact, one-third of study participants were unable to recall the exact name of the antibiotic they received. The authors did not precisely distinguish between single-agent sulfonamides and the combination drug, trimethoprim-sulfamethoxazole, although it seems reasonable to assume that the majority of the prescriptions were for the latter. Finally, given the observational nature of the study, the authors could not be certain that the observed associations were due to the antibiotic, the infection for which the drug was prescribed, or another confounding factor. ●

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VALUE-BASED MEDICINE: PART 3

The role of patient-reported outcomes in women's health

Patient-reported outcomes, obtained with a validated survey instrument, are critical to improving clinical research, health care quality, and patient care. Using them in women's health care will benefit both patients and clinicians. Here's how.

Kimberly D. Gregory, MD, MPH; Lisa M. Korst, MD, PhD; Samia Saeb, MPH; and Moshe Fridman, PhD

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In its landmark publication, "Crossing the quality chasm: A new health system for the 21st century," the Institute of Medicine (now the National Academy of Medicine) called for an emphasis on patient-centered care that it defined as "Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions."[1] Studies suggest that the patient's view of health care delivery determines outcome and satisfaction.[2] Therefore, we need to expend more effort to understand what patients need or want from their treatment or interaction with the health care system.

Measuring patient-reported outcomes (PROs) is an attempt to recognize and address patient concerns. Although currently PROs are focused primarily in the arena of clinical research, their use has the potential to transform daily clinical patient encounters and improve the cost and quality of health care.[3]

In this article, we provide a brief overview of PROs and describe how they can be used to improve individual patient care, clinical research, and health care quality. We also offer examples of how PROs can be used in specific women's health conditions.

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Developed in collaboration with the American College of Obstetricians and Gynecologists

What exactly are PROs?

PROs are reports of the status of a patient's health condition, health behavior, or experience with health care; they come directly from the patient, without anyone else (such as a clinician or caregiver) interpreting the patient's response.[4] PROs usually pertain to general health, quality of life, functional status, or preferences associated with health care or treatment.[5] Usually PROs are elicited via a self-administered survey and provide the patient's perspective on treatment

benefits, side effects, change in symptoms, general perceptions of feelings or well-being, or satisfaction with care. Often they represent the outcomes that are most important to patients.[6] The survey usually consists of several questions or items. It can be general or condition specific, and it may represent one or more health care dimensions.

The term *patient-reported outcome measure* (PROM) refers to the survey instrument used to collect PROs. *Patient-reported experience measures* (PREMs), such as satisfaction surveys, are considered a subset of PROMs.[7]

Standardized PROs developed out of clinical trials

The use of PROs evolved from clinical trials. The proliferation of PROs resulted in an inability to compare outcomes across trials or different conditions. This led to a need to standardize and possibly harmonize measures and to reach consensus about properties required for a "good" measure and requirements needed for "adequate" reporting. Many investigators and several national and international organizations have provided iterative guidance, including the US Food and Drug Administration (FDA), European Medicines Agency, National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS), International Consortium for Health Outcomes Measurement (ICHOM), University of Oxford Patient Reported Outcomes Measurement Group, Cochrane Systematic Reviews, Consolidated Standards of Reporting Trials–Patient Reported Outcomes (CONSORT-PRO) extension (how to report PROs with the CONSORT checklist), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[4,5,8–18]

In the United States, the RAND Medical Outcomes Study led to the development of the 12- and 36-item short form surveys, which are widely recognized and commonly used PROMs for health-related quality of life.[19] The study generated multiple additional survey instruments that evaluate other domains and dimensions of health. These surveys have been translated into numerous languages, and the RAND website lists over 100 publications.[19]

FAST TRACK

PROs often represent the outcomes that are most important to patients

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ILLUSTRATION: PAUL ZWOLAK FOR OBG MANAGEMENT

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In 2002, the NIH sponsored PROMIS, a cooperative program designed to develop, validate, and standardize item banks to measure PROs that were relevant across multiple, common medical conditions. Based on literature review, feedback from both healthy and sick patients, and clinical expert opinion, the PROMIS investigators developed a consensus-based framework for self-reported health that included the following domains: pain, fatigue, emotional distress, physical functioning, and social role participation; these domains were evaluated on paper or with computer-assisted technology.[11–14] PROMIS is now a web-based resource with approximately 70 domains pertinent to children and adults in the general population and in those with chronic disease. Measures have been translated into more than 40 languages, and PROMIS-related work has resulted in more than 400 publications.[14]

In 2006, the FDA issued a draft document regarding the PRO standards that should be included in clinical trials for consideration of drug and device applications (**TABLE 1**). These recommendations, updated in 2009, were largely drawn from work published by PROMIS and University of Oxford investigators.[4,14,16]

Because PROs are infrequently measured in routine clinical practice and PROMs that are used vary between countries, global comparison is difficult. Hence, ICHOM convened in 2012 to develop consensus-based, globally agreed on sets of outcomes that are intended to reflect what matters most to patients.

ICHOM specified 2 goals: 1) the core sets should be used in routine clinical practice, and 2) the core sets should be used as end points in clinical studies.[15]

As of May 2015, 12 standard sets of outcomes have been developed, representing 35% of the global burden of disease. ICHOM currently is creating networks of hospitals around the world to begin measuring, benchmarking, and performing outcome comparisons that can ultimately be used to inform global health system learning and clinical care improvement.[15]

FAST TRACK

With today's focus on patient-centered care, there is a growing mandate to integrate PROMs into clinical care, quality improvement, and ultimately reimbursement

Use of PROs is evolving

Historically, PROMs have been used primarily in clinical trials to document the relative benefits of an intervention. With today's focus on patient-centered care, however, there is a growing mandate to integrate PROMs into clinical care, quality improvement, and ultimately reimbursement. Recently, Basch and colleagues eloquently described the benefit of routine collection of PROs for cancer patients and the opportunity for improved care across the health system.[20]

PROs can be applied on various levels. For example, if a patient reports a symptom (X), or a change in symptom X, the following options are possible:

- **Clinician level:** Symptom management with altered dose or change in medication. This is associated with improved self-efficacy for the patient, a shift toward goal-oriented care, improved communication with the provider, and improved patient satisfaction.
- **Researcher level:** PROs should be used as a primary end point, in addition to traditional outcomes (mortality, survival, physiologic markers), to allow for comparative effectiveness studies or patient-centered outcomes research studies that evaluate what matters most to patients relative to the specific health condition, intervention, and symptom management.
- **Health system level:** Quality assurance, quality improvement activities. How effective is the health system in the management of symptom X? Are all clinicians using the same medication or the same dose? Is there a best practice for managing symptom X?
- **Population level:** Provides evidence for other clinicians and patients to make decisions about what to expect with treatment for symptom X.

From a reimbursement level, clinicians and providers are paid based on performance—the more satisfied patients are about X, the higher the reimbursement. This has been pertinent particularly in high-volume orthopedic conditions in which anatomic correction of hip or knee joints has not

TABLE 1 **PRO standards recommended for inclusion in clinical trials for consideration of drug and device applications**[4,14,16]

Criteria to consider in PRO development	Comment
Appropriateness	• Does content address relevant questions for device or drug? • Were patients (and their concerns) included in the development of the conceptual framework?
Acceptability	• Is the questionnaire acceptable to patients? • How is it being administered (paper, electronic)? • Timing after intervention? • How long does it take? • Frequency of administration? • Language?
Feasibility	• Is it easy to administer, easy to analyze? • Cost? • Staff training? • Does it interrupt workflow?
Interpretability	• Are the scores easy to interpret? • What is the minimal clinically important difference from the patient perspective?
Precision	• How precise are the scores? • How is it scaled? Visual analog? Likert? Categorical? Weighting?
Reliability	• Are the results internally consistent and reproducible (test/re-test)?
Validity	• Does the questionnaire measure what it claims to measure? • Targeted patient population acknowledges face/content validity? • Criterion validity—correlates with another measure (if there is one) • Construct validity
Responsiveness	• Does it detect changes over time (after treatment) that matter to patients? • Does it detect differences in disease states? • What is the minimal clinically meaningful effect or change?

Abbreviation: PRO, patient-reported outcome.

consistently demonstrated improvement in quality of life as measured by the following PROs: perception of pain, mobility, physical functioning, social functioning, and emotional distress. Because of concerns about high volume, high cost, and inconsistent outcomes, the US Department of Health and Human Services has specified that 50% of Medicare and 90% of Medicaid reimbursements will be based on outcomes or value-based purchasing options.[21]

Studies have shown that it is possible to collect PRO data for cancer patients—despite age or severity of illness—and integrate it into clinical care delivery. These data can provide useful, actionable information, resulting in decreased emergency department visits, longer toleration of chemotherapy, and improved survival.[22] Similar results have been demonstrated in other medical conditions, although challenges exist when transitioning from research settings to routine care. Challenges include privacy concerns, patient recruitment and tracking,

encouraging patients to complete the PRO surveys (nonresponse leads to biased data), real and perceived administrative burden to staff, obtaining clinician buy in, and costs related to surveys and data analysis.[23]

Using PROs in women's health care: Benefits for patients and clinicians

According to a study by Frosch, patients want to know if a prescribed therapy actually improves outcomes, not whether it changes an isolated biomarker that does not translate into subjective improvement.[24] They want to know if the trade-off (adverse effects or higher cost) associated with a new drug or therapy is worth the improved mobility or time spent pain free.

Intuitively, all clinicians have similar opportunities for discussions with regard to the risks, benefits, and alternatives of medical treatment, surgical treatment, or expectant management. We routinely document this discussion daily. However, in this era of patient-centered care, when a patient asks, "What should I do, doctor?" we no longer can respond with a default recommendation. We must engage the patient and ask, "What do you want to do? What is most important to you?"

FAST TRACK

ObGyns are well suited to benefit from standardized efforts to collect PROs, as we frequently discuss with our patients trade-offs regarding treatment risks and benefits and their personal values and preferences

ObGyns are well suited to benefit from standardized efforts to collect PROs, as we frequently discuss with our patients trade-offs regarding treatment risks and benefits and their personal values and preferences. Examples include contraception options, hormone treatment for menopause, medication use during pregnancy, decisions at the limits of viability, preterm delivery for severe preeclampsia, induction/augmentation versus spontaneous labor, epidural versus physiologic labor, repeat cesarean versus vaginal birth after cesarean, and even elective primary cesarean versus vaginal birth.

Validated PROMs exist for benign gynecology, such as abnormal uterine bleeding, fibroids, polycystic ovary syndrome (PCOS), infertility, pelvic organ prolapse and/or urinary incontinence, and surgery for benign gynecology symptoms, as well as for cancer (breast, ovarian, cervical).[25–39]

From the PCOS literature we can glean a poignant example of the importance of PROs. Martin and colleagues compared patient and clinician interviews regarding important PROs from the patient perspective.[29] Patients identified pain, cramping, heavy bleeding, and bloating as important, whereas clinicians did not consider these symptoms important to patients with PCOS. Clinicians thought "issues with menstruation," characterized as irregular or no periods, were important, whereas patients were more concerned with heavy bleeding or bleeding of long duration. The authors concluded that concepts frequently expressed by patients and considered important from their perspective did not register with clinicians as being relevant and are not captured on current PRO instruments, emphasizing our knowledge gap and the need to pay attention to what patients want.[29]

Surprisingly, although pregnancy and childbirth is the number one cause for hospital admissions, a highly preference-driven condition, and a leading cause of morbidity, mortality, and costs, there are few published PROs in the field. In a systematic review of more than 1,700 articles describing PROs published in English through 2014, Martin found that fewer than 1% included PROs specific to pregnancy and childbirth.[40]

ICHOM has created a standard set of outcomes for pregnancy and childbirth based on consensus recommendations from physicians, measurement experts, and patients.[41] The consortium describes 4 domains and 14 subdomains (**TABLE 2**) and provides suggestions for a validated PROM if known or where appropriate.

Similar domains and subdomains have been corroborated by our research team (the Maternal Quality Indicator [MQI] Work Group), the Childbirth Connection, and Gartner and colleagues.[42–44] The MQI Work Group recently conducted a national survey of what women want and what they think is important for their childbirth experience. We identified

TABLE 2 ICHOM standard set of outcomes for pregnancy and childbirth[41]

Domains	Survival	Morbidity	Patient-reported health and well-being	Patient satisfaction with care
Subdomains	Maternal mortality	Severe maternal morbidity	Health-related quality of life	Satisfaction with results of care
	Neonatal mortality	Neonatal morbidity	Postpartum depression	Shared decision making and confidence in care providers
		Preterm birth	Maternal confidence and success with breastfeeding	Birth experience
			Pelvic pain and dysfunction	
			Mother-infant attachment	
			Confidence with role as a mother	

Abbreviation: ICHOM, International Consortium for Health Outcomes Measurement.

19 domains, consistent with those of other investigators.[42] Gartner and colleagues advocate for a composite outcome measure that combines the core domains into one preference-based utility measure that is weighted.[44] The rationale for this recommendation is that the levels of the domains might contribute differently to the overall birth experience. For example, *communication* might contribute more to an overall measure than *pain management*.[44] The development of a childbirth-specific survey to evaluate patient-reported outcomes and patient-reported experiences with care is needed if we are to provide value-based care in this arena.[45]

Looking forward

PROs, PROMs, and PREMs are here to stay. They no longer are limited to clinical research, but increasingly will be incorporated into clinical care, providing us with opportunities to improve the quality of health care delivery, efficiency of patient/clinician interactions, and patients' ratings of their health care experience. ●

FAST TRACK

Development of a childbirth-specific survey to evaluate patient-reported outcomes and experiences with care is needed if we are to provide value-based care in this arena

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UPDATE Gynecologic cancer

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The author reports no financial relationships relevant to this article.

Gynecologic malignancies remain a major cause of morbidity and mortality. In this article: latest cervical cancer screening recommendations from the USPSTF, and 2 endometrial cancer news items, on SLN biopsy and PD-1 blockade immunotherapy.

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In this Update, I report on the latest US Preventive Services Task Force (USPSTF) cervical cancer screening recommendations. In addition, I describe the results of 2 studies, a large prospective multicenter study of the accuracy of sentinel lymph node (SLN) biopsy in endometrial cancer, and a proof-of-concept review of use of checkpoint blockade to increase immune response and of its possible role in endometrial cancer.

hrHPV testing used alone as primary screening for cervical cancer: USPSTF recommendations

US Preventive Services Task Force. Draft recommendation statement: cervical cancer: screening. https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2. Published October 2017. Accessed February 5, 2018.

Despite our rapid advances in understanding the molecular underpinnings of cancer, gynecologic malignancies are still a major cause of morbidity and mortality among women. Cervical cancer stands as an example of how a cancer screening test can be implemented to reduce mortality. In this section, I report on the USPSTF cervical cancer screening recommendations, which were updated in October 2017.

Even with the widespread implementation of screening programs for cervical cancer in the United States, 13,240 women will be diagnosed with the disease in 2018, and 4,170 will die from cervical cancer.[1] Most often, cervical cancer occurs in women who have not been adequately screened. It is now recognized that the human papillomavirus (HPV) is the cause of cervical cancer.[2]

While cervical cytology has long been used as a screening test for cervical cancer, testing for high-risk HPV subtypes (hrHPV testing) also has been used as a screening modality. Traditionally, hrHPV testing is used

in combination with cervical cytology, so called cotesting. There is convincing evidence that cervical cytology, as well as strategies that use hrHPV testing, can detect high-grade cervical precancers and cancers and thereby reduce mortality. However, cervical cancer screening is also associated with frequent follow-ups, invasive procedures performed to assess abnormal results, psychological distress, and adverse pregnancy outcomes of treatment for precancerous lesions.

The USPSTF based its new cervical cancer screening recommendations on clinical trial data and decision modeling of various screening strategies, and weighed the benefits and harms of each strategy.

Recommendations from the USPSTF

hrHPV screening for cervical cancer. The USPSTF recommends screening with cervical cytology every 3 years for women 21 to 29 years of age. For women 30 to 65 years of age, screening with cytology every 3 years, or hrHPV testing alone used every 5 years, is recommended.

Data from large randomized trials suggest cytologic screening is slightly less sensitive than hrHPV testing in detecting high-grade (grade 2 or 3) cervical intraepithelial neoplasia (CIN). However, hrHPV testing results in more follow-up tests and colposcopies. In a decision model, the USPSTF found that cotesting increased the number of follow-up tests but did not increase detection of grade 3 CIN or invasive cancer. This is the first clinical guideline to recommend hrHPV testing used alone for screening. The American College of Obstetricians and Gynecologists (ACOG) continues to recommend cotesting (cytology in combination with hrHPV) as a primary screening modality in this population.[3]

Exceptions. According to the USPSTF, 3 populations should not be screened: women over 65 years of age with adequate prior screening who are not otherwise at high risk for cervical cancer; women under 21 years of age; and women who have had a hysterectomy and do not have a history of grade 2 or 3 CIN or cancer.

Summary. The USPSTF recommendations are intended for the general population and are not applicable to women with a history of high-grade CIN or cervical cancer, women with in utero exposure to diethylstilbestrol, and women who are immunocompromised. The remaining USPSTF recommendations are largely in line with guidelines published by ACOG and other groups.[3,4]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Testing for high-risk HPV alone is a reasonable screening option for cervical cancer. This modality can be used in women 30 to 65 years of age but should not be repeated more frequently than every 5 years in those with a negative result.

FAST TRACK

For women aged 21 to 29, screening with cervical cytology every 3 years is recommended by the USPSTF. For women aged 30 to 65, testing for high-risk HPV is a reasonable screening option to cervical cytology.

SLN biopsy for staging endometrial cancer

Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384–392.

Surgery is the cornerstone of treatment for most gynecologic cancers. The widespread use of minimally invasive surgical techniques and the introduction of less radical procedures for gynecologic cancers have helped reduce surgical morbidity.

For endometrial cancer, the role of lymphadenectomy is controversial. Data from prospective trials of this procedure suggest an association with increased morbidity and long-term sequelae, such as lymphedema, and no association with improved survival.[5,6]

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SLN biopsy is an important advance and a potential alternative nodal evaluation method that may be associated with decreased morbidity. In this more limited assessment technique, the first nodal drainage basins of a tumor are identified and removed for pathologic evaluation.

Accuracy of SLN biopsy in endometrial cancer was the subject of Rossi and colleagues' recent large prospective multicenter study, the Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial.

Details of the study

Rossi and colleagues conducted the FIRES trial to estimate the sensitivity of SLN biopsy in detecting nodal metastases in women with stage I endometrial cancer. Patients (N = 385) from 10 US sites were enrolled in the study. SLN evaluation was performed after cervical injection of indocyanine green followed by robotic-assisted hysterectomy. After identification of the SLN, participants underwent pelvic lymphadenectomy. Performance of para-aortic lymphadenectomy was optional.

Mapping of the SLN was feasible in 86% of patients, including bilateral mapping in 52%. Twelve percent of the participants had nodal metastases. SLN biopsy had a sensitivity of 97% in women who had identification of the SLNs. Similarly, the negative predictive value was high, 99.6%. The procedure was associated with acceptable short-term toxicity with adverse events in 9% of study participants. Common complications included neurologic complications, respiratory distress, nausea and vomiting, and, in 3 patients, bowel injury.

Accurate detection of nodal metastases. Results of the study suggest SLN biopsy is accurate in detecting nodal metastases in women with endometrial cancer. Although long-term toxicity was not examined, other work suggests the lymphedema rates associated with SLN biopsy may be lower than those of lymphadenectomy. While the study described impressive performance characteristics, there remain technical challenges. Even among skilled surgeons trained for the protocol, there was no nodal mapping in nearly half of the women with endometrial cancer. Women without node mapping require full lymphadenectomy thus negating the possible benefits of the procedure.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Given the high accuracy of SLN mapping in endometrial cancer, the procedure likely will become the standard of care for nodal evaluation by gynecologic oncologists.

FAST TRACK

SLN biopsy was 97% sensitive in detecting nodal metastases in women with stage I endometrial cancer, and the procedure likely will become standard of care for nodal evaluation

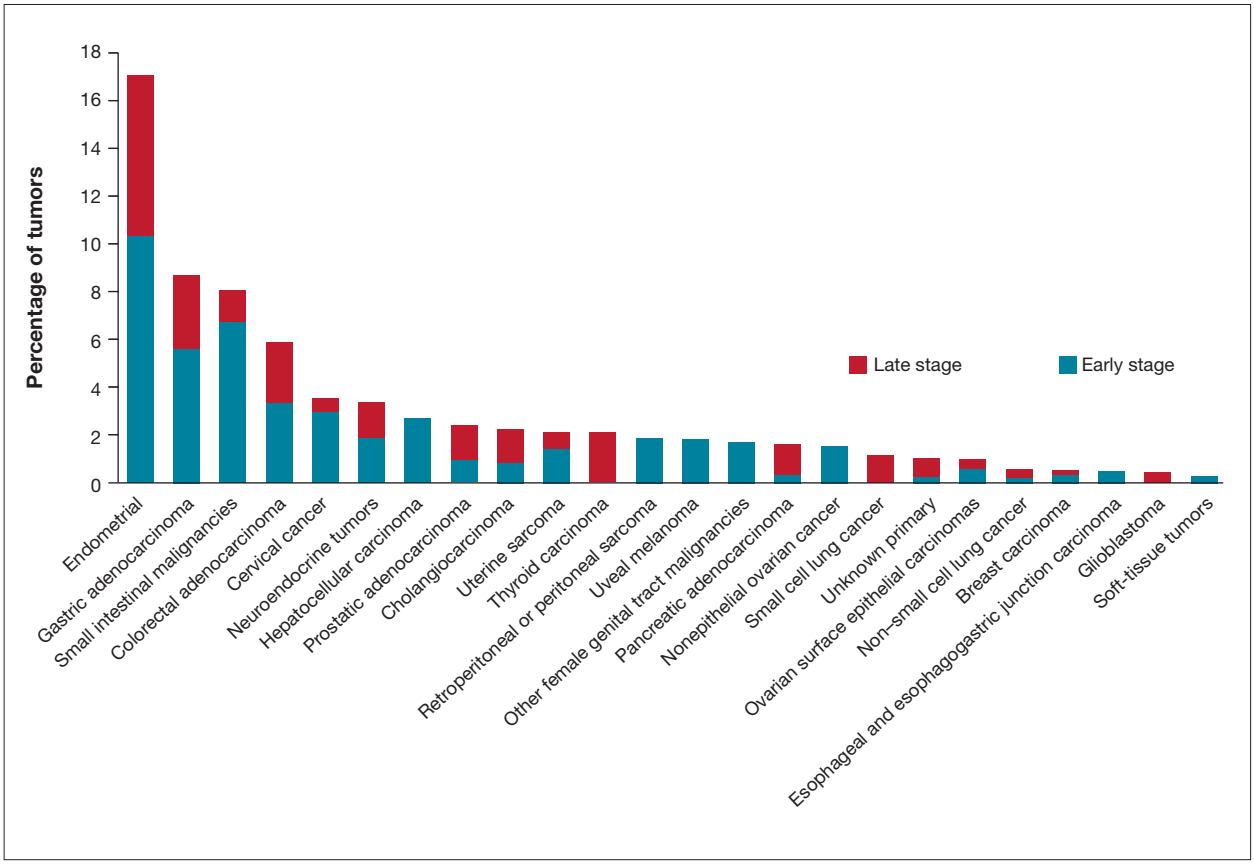
Immunotherapy for gynecologic cancers

Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–413.

In oncology, precision medicine is rapidly becoming a standard treatment approach. Therapies are being used to target specific genetic alterations in tumors. In cancer immunotherapy, the immune system is being used to facilitate clearance of cancer cells.

The most common mechanism of action of clinically used immunotherapeutic agents is blockade of programmed cell death protein 1 (PD-1), a lymphocyte receptor that prevents the immune system from targeting the body's own cells.[7] Cancers that have mutations in the DNA mismatch repair (MMR) proteins display microsatellite instability (MSI) and produce high levels of abnormal proteins.[8] These abnormal proteins serve as tumor antigens that can be targeted by the body's normal immune system.

FIGURE Mismatch-repair deficiency across 12,019 tumors



Percentage of tumors deficient in mismatch repair in each cancer subtype. Deficient tumors were identified in 24 of 32 subtypes tested, more often in early disease (pre–stage IV).

SOURCE: Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–413. Used with permission.

In May 2017, the US Food and Drug Administration (FDA) granted accelerated approval of the PD-1 blocking antibody pembrolizumab for the treatment of unresectable or metastatic MSI-high (MSI-H) or MMR-deficient solid tumors.[9] The approval was based on data from 149 patients treated in 5 studies that demonstrated a response rate of 39.6%, including responses that lasted at least 6 months in 78% of participants. This was the first ever cancer drug that received FDA approval based on a tumor's biomarker profile without regard to the site of origin. I describe the results of a study by Le and colleagues that examines the possible role of immunotherapy in a variety of solid tumors in this section.

Details of the study

This study examined the clinical efficacy of PD-1 blockade in 86 patients with advanced, MMR-deficient tumors from 12 different sites. Endometrial cancer was the second most frequent primary tumor site in 17% of patients. Within the cohort, the overall objective response rate was 53%, which included 21% of patients with complete radiographic response (no imaging evidence of cancer). Disease control, either complete or partial response or stable disease, was achieved in 77% of patients. After a median follow-up of 12.5 months, neither the median progression-free survival (PFS) nor median overall survival had been reached. The authors estimated that 2-year overall survival was 64%,

substantially higher than expected for patients with advanced solid tumors.

Le and colleagues also performed several in vivo laboratory experiments to explore the mechanisms by which patients responded. In addition, they used sequencing to determine the prevalence of MMR deficiency in 12,019 cancer samples that included 32 distinct tumor types (**FIGURE,** page 27). Endometrial cancer had the highest frequency of MMR deficiency (17%). Four percent of cervical cancers and less than 2% of ovarian cancers were MMR-deficient.

The promise of immunotherapy for endometrial cancer. This study's data and other emerging data have important implications for women with gynecologic cancer, particularly endometrial cancer. First, given the frequency of MMR mutations among women with endometrial cancer, MMR testing should be strongly considered for these patients. Many institutions have protocols for reflex testing with immunohistochemistry for women with endometrial cancer. For women with positive test results, germline sequencing can be performed to determine if they have an inherited MMR deficiency, Lynch syndrome. Presence of an MMR deficiency is an important factor in cancer screening and potential treatment.

Second, the impressive results of PD-1 blockade in patients with MMR-deficient tumors suggest that this treatment strategy may be important for women with recurrent or metastatic endometrial cancer. The ideal timing of immunotherapy for women with endometrial cancer is an area of active ongoing study. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Immunotherapy with PD-1 blockade is an important treatment strategy for women with MMR-deficient or MSI-H gynecologic cancers.

FAST TRACK

Given the frequency of MMR mutations among women with endometrial cancer, MMR testing should be strongly considered for these patients

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Factors critical to reducing US maternal mortality and morbidity

ACOG is working to eliminate preventable maternal mortality with an all-hands-on-deck approach through its AIM Program and other collaborative initiatives with clinicians, public health officials, hospitals, and patient safety organizations

Lucia DiVenere, MA

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Maternal mortality statistics
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More women die from pregnancy complications in the United States than in any other developed country. The United States is the only industrialized nation with a rising maternal mortality rate.

Those 2 sentences should stop us all in our tracks.

In fact, the United States ranks 47th globally with the worst maternal mortality rate. More than half these deaths are likely preventable, with suicide and drug overdose the leading causes of maternal death in many states. All this occurs despite our advanced medical system, premier medical colleges and universities, embrace of high-tech medical advances, and high percentage of gross domestic product spent on health care.

Need more numbers? According to a 2016 report in *Obstetrics and Gynecology*, the United States saw a 26% increase in the maternal mortality rate (unadjusted) in only 15 years: from 18.8 deaths per 100,000 live births in 2000 to 23.8 in 2014 (**FIGURE 1,** page 32).[1]

This problem received federal attention when, in 2000, the US Department of Health and Human Services launched Healthy People 2010. That health promotion and disease prevention agenda set a goal of reducing maternal mortality to 3.3 deaths per 100,000 live births by 2010, a goal clearly not met.

Considerable variations by race and by state

The racial disparities in maternal mortality are staggering and have not improved in more than 20 years: African American women are 3.4 times more likely to die than non-Hispanic white women of pregnancy-related complications. In 2011–2013, the maternal mortality ratio for non-Hispanic white women was 12.7 deaths per 100,000 live births compared with 43.5 deaths for non-Hispanic black women (**FIGURE 2,** page 32).[2] American Indian or Alaska Native women, Asian women, and some Latina women also experience higher rates than non-Hispanic white women. The rate for American Indian or Alaska Native women is 16.9 deaths per 100,000 live births.[3]

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The author reports no financial relationships relevant to this article.

Some states are doing better than others, showing that there is nothing inevitable about the maternal mortality crisis. Texas, for example, has seen the highest rate of maternal mortality increase. Its rate doubled from 2010 to 2012, while California reduced its maternal death rate by 30%, from 21.5 to 15.1, during roughly the same period.[1]

This is a challenge of epic proportions, and one that the American College of Obstetricians and Gynecologists (ACOG), under the leadership of President Haywood Brown, MD, and Incoming President Lisa Hollier, MD, is determined to meet, ensuring that a high maternal death rate does not become our nation's new normal.

Dr. Brown put it this way, "ACOG collaborative initiatives such as Levels of Maternal Care (LOMC) and implementation of OB safety bundles for hemorrhage, hypertension, and thromboembolism through the AIM [Alliance for Innovation on Maternal Health] Program target maternal morbidity and mortality at the community level. Bundles have also been developed to address the disparity in maternal mortality and for the opiate crisis."

ACOG is making strides in putting in place nationwide meaningful, evidence-driven systems and care approaches that are proven to reduce maternal mortality and morbidity, saving mothers' lives and keeping families whole.

ACOG's AIM Program established to make an impact

The AIM Program (www.safehealthcareforeverywoman.org) is bringing together clinicians, public health officials, hospital administrators, patient safety organizations, and advocates to eliminate preventable maternal mortality throughout the United States. With funding and support from the US Health Resources and Services Administration, AIM is striving to:

- reduce maternal mortality by 1,000 deaths by 2018
- reduce severe maternal morbidity
- assist states and hospitals to improve outcomes
- create and encourage use of maternal safety bundles (evidence-based tool kits to guide the best care).

AIM offers participating physicians and hospitals online learning modules, checklists, work plans, and links to tool kits and published resources. Implementation data is shared with hospitals and states to further improve care. Physicians participating in AIM can receive Part IV maintenance of certification; continuing education units will soon be offered for nurses. In the future, AIM-participating hospitals may be able to receive reduced liability protection costs, too.

To date, 17 states are participating in the AIM initiative (**FIGURE 3,** page 32), with more states ready to enroll.[4] States must demonstrate a commitment to lasting change to participate. Each AIM state must have an active maternal mortality review committee (MMRC); committed leadership from public health, hospital associations, and provider associations; and a commitment to report AIM data.

AIM thus far has released 9 obstetric patient safety bundles, including:

- reducing disparities in maternity care
- severe hypertension in pregnancy
- safe reduction of primary cesarean birth
- prevention of venous thromboembolism
- obstetric hemorrhage
- maternal mental health
- patient, family, and staff support following a severe maternal event
- postpartum care basics
- obstetric care of women with opioid use disorder (in use by Illinois, Massachusetts, Maryland, New Jersey, Maine, New Hampshire, Vermont, New York, Ohio, Oklahoma, Tennessee, Texas, and Virginia).

Review committees are critical to success

In use in many states, MMRCs are groups of local ObGyns, nurses, social workers, and other health care professionals who review specific cases of maternal deaths from their local area and recommend local solutions to prevent future deaths. MMRCs can be a

FAST TRACK

AIM offers participating physicians and hospitals online learning modules, checklists, work plans, and links to tool kits and published resources

FIGURE 1 Adjusted US maternal mortality rates, 2000–2014[1]

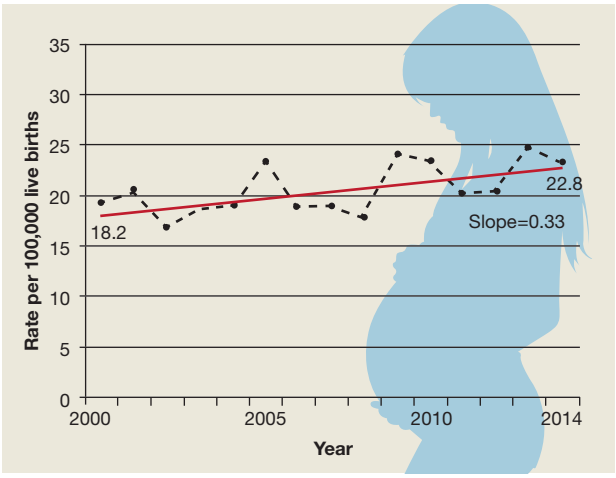


FIGURE 2 US maternal mortality ratio by race, 2011–2013[2]

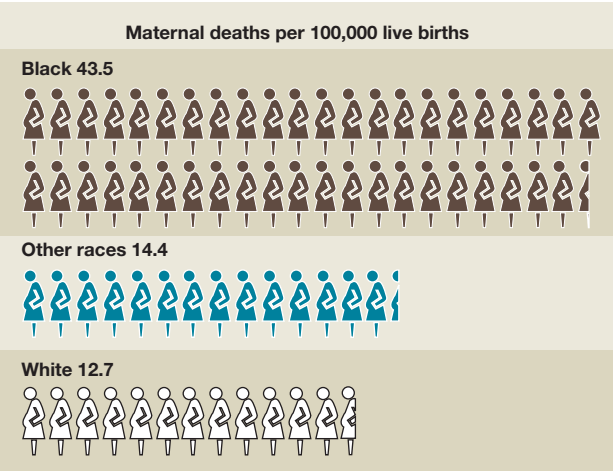
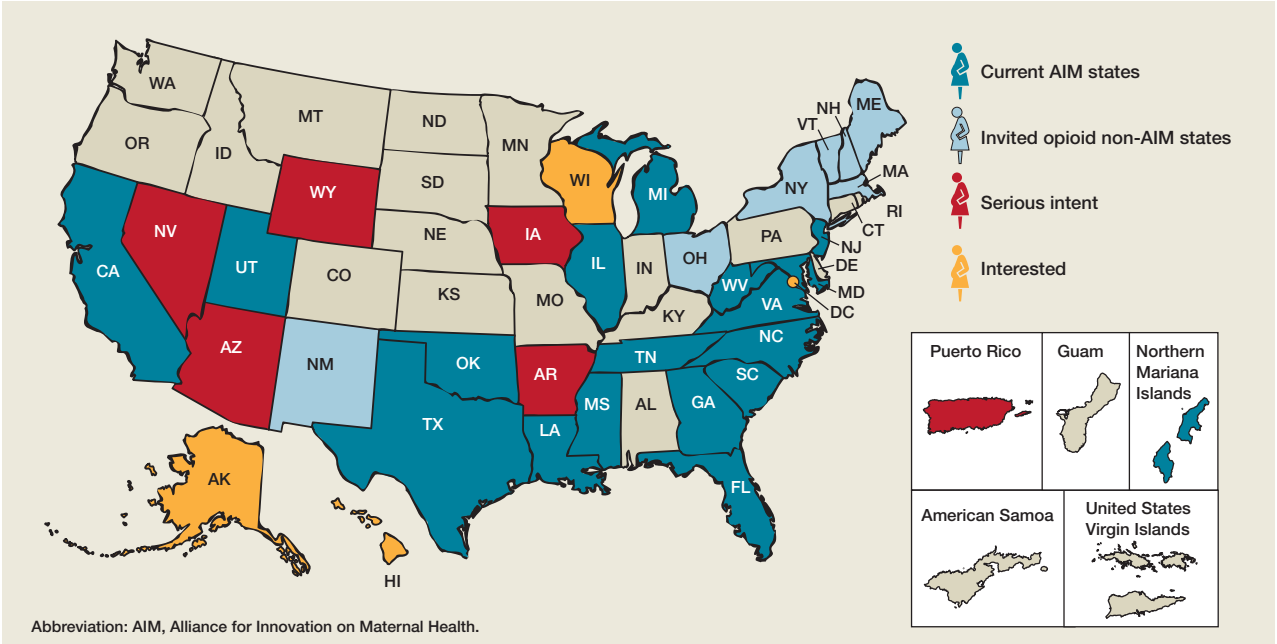


FIGURE 3 States, hospital networks, and other countries currently participating in the AIM Program[4]

AIM states				AIM networks	AIM countries
California	Maryland	North Carolina	Texas	National Perinatal Information Center	Malawi
Florida	Michigan	Oklahoma	Utah	Premier	Northern Mariana Islands
Georgia	Mississippi	South Carolina	Virginia	Trinity Health Care	
Illinois	New Jersey	Tennessee	West Virginia		
Louisiana					



Abbreviation: AIM, Alliance for Innovation on Maternal Health.

critically important source of data to help us understand the underlying causes of maternal mortality.

Remember California's success in reducing its maternal mortality rate, previously mentioned? That state was an early adopter of an active MMRC and has worked to bring best practices to maternity care throughout the state.

While every state should have an active MMRC, not every state does. ACOG is working with states, local leaders, and state and federal legislatures to help develop MMRCs in every state.

Dr. Brown pointed out that, "For several decades, Indiana had a legislatively authorized multidisciplinary maternal mortality review committee that I actively participated in and led in the late 1990s. The authorization for the program lapsed in the early 2000s, and the Indiana MMRC had to shut down. Bolstering the federal government's capacity to help states like Indiana rebuild MMRCs, or start them from scratch, will help state public health officials, hospitals, and physicians take better care of moms and babies."

Dr. Hollier explained, "In Texas, I chair our Maternal Mortality and Morbidity Task Force, which was legislatively authorized in 2013 in response to the rising rate of maternal death. The detailed state-based maternal mortality reviews provide critical information: verification of vital statistics data, assessment of the causes and contributing factors, and determination of pregnancy relatedness. These reviews identify opportunities for prevention and implementation of the most appropriate interventions to reduce maternal mortality on a local level. Support of essential review functions at the federal level would also enable data to be combined across jurisdictions for national learning that was previously not possible."

Pending legislation will strengthen efforts

ACOG is working to enact into law the Preventing Maternal Deaths Act, HR 1318 and S1112. This is bipartisan legislation under which the Centers for Disease Control and Prevention would help states create or expand MMRCs and will require the Department of Health and Human Services to research ways to reduce disparities in maternal health outcomes. ●

Acknowledgement

The author thanks Jean Mahoney, ACOG's Senior Director, AIM, for her generous assistance.

FAST TRACK

ACOG is working with states, local leaders, and state and federal legislatures to help develop MMRCs in every state

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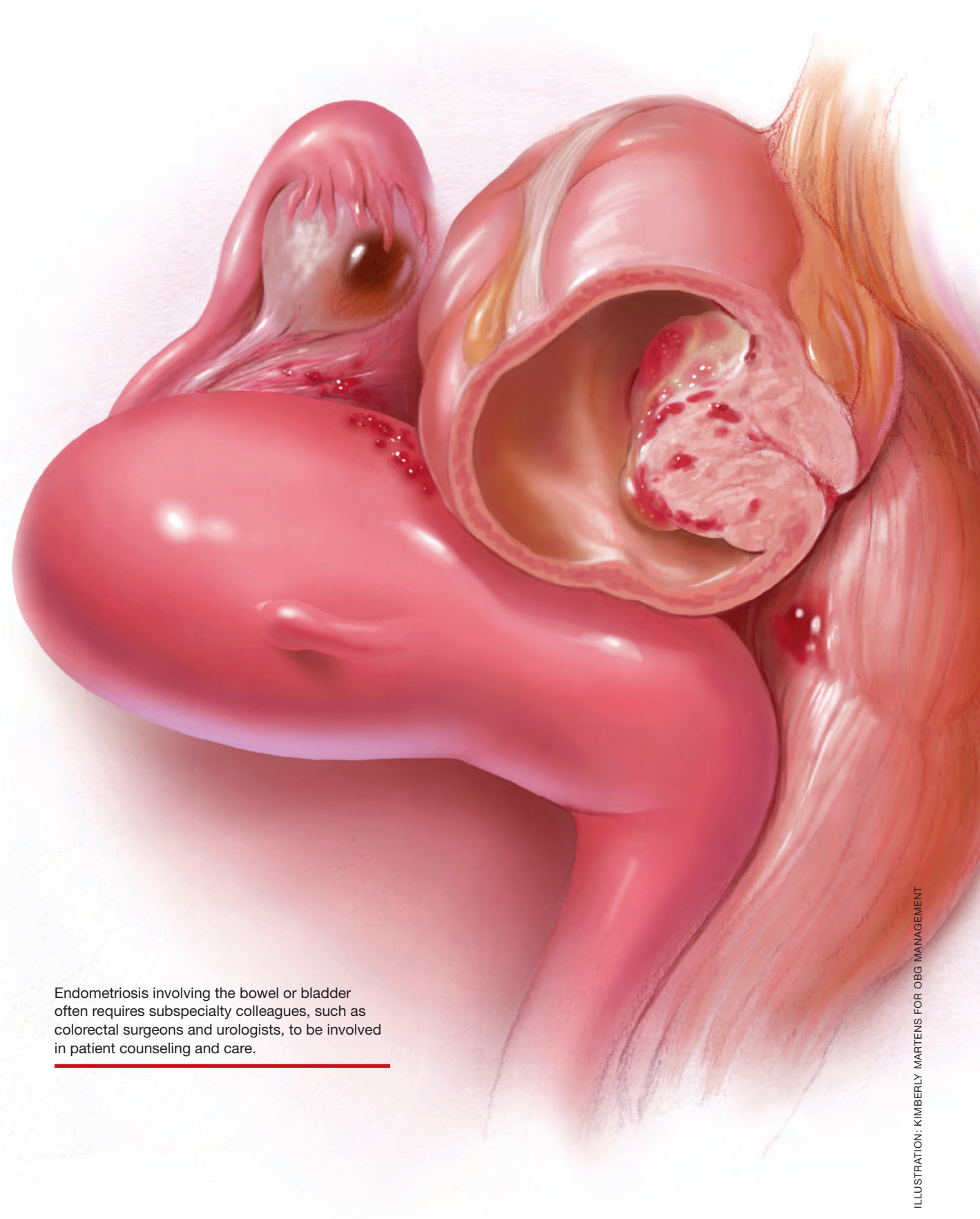

Endometriosis involving the bowel or bladder often requires subspecialty colleagues, such as colorectal surgeons and urologists, to be involved in patient counseling and care.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

ROUNDTABLE

Endometriosis: Expert perspectives on medical and surgical management

Challenging to manage, endometriosis requires a thorough understanding of the disease process, first- and second-line therapies, and multidisciplinary care

Expert panel featuring Arnold P. Advincula, MD; Douglas N. Brown, MD; and Hye-Chun Hur, MD, MPH

Endometriosis is one of the more daunting diagnoses that gynecologists treat. In this roundtable discussion, moderated by OBG Management Board Member Arnold P. Advincula, MD, 2 leading surgeons discuss endometriosis diagnosis as well as medical and surgical management.

Take-home points

- Endometriosis management involves fluidity of care. Treatment approaches will change throughout a patient's reproductive life, depending on the patient's presenting symptoms and reproductive goals.
- Inform the patient of the disease process and how it may affect her menstrual pain symptoms and family planning.
- Educate patients so they may effectively participate in the management discussion. Hear the voice of the patient to make a tailored plan of care for each individual.
- Endometriosis can be a complex medical problem. Use a comprehensive multidisciplinary approach when appropriate.

First-time evaluation

Arnold P. Advincula, MD: When a patient presents to your practice for the first time and you suspect endometriosis, what considerations tailor your evaluation, and what does that evaluation involve?

Hye-Chun Hur, MD, MPH: The diagnosis is contingent on a patient's presenting profile. How symptomatic is she? How old is she? What are her reproductive goals? The gold standard for diagnosis is a histologic diagnosis, which is surgical. Depending on the age profile, however, and how close she is to menopause, the patient may be managed medically. Even women in the young reproductive age group may be managed medically if symptoms are responsive to medical treatment.

Douglas N. Brown, MD: I agree. When a patient presents without a laparoscopy, or a tissue diagnosis, but the symptoms are consistent with likely endometriosis (depending on where she is in her reproductive cycle and what her goals are), I think treating with a first-line therapy—hormonal treatments such as progestin-only oral contraceptive pills—is acceptable. I usually conduct a treatment trial period of 3 to 6 months to see if she obtains any symptom relief.

If that first-line treatment fails, generally you can move to a second-line treatment.

I have a discussion in which I either offer a second-line treatment, such as medroxyprogesterone (Depo-Provera) or leuprolide acetate (Lupron Depot), or get a tissue diagnosis, if possible, by performing laparoscopy. If first-line or even second-line therapy fails,

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OBG Management Expert Panel

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Dr. Advincula reports being a consultant to AbbVie, Applied Medical, ConMed, CooperSurgical, Intuitive Surgical, and Titan Medical and receiving royalties from CooperSurgical. Dr. Brown reports being a consultant to Medtronic and CooperSurgical. Dr. Hur reports no financial relationships relevant to this article.

you need to consider doing a diagnostic laparoscopy to confirm or deny the diagnosis.

Dr. Advincula: Are there any points in the evaluation of a patient who visits your practice for the first time where you would immediately offer a surgical approach, as opposed to starting with medical management?

Dr. Hur: A large percentage of my patients undergo surgical evaluation, as surgical diagnosis is the gold standard. If you look at the literature, even among surgeons, the accuracy of visual diagnosis is not great.[1,2] I target individuals who are either not responsive to medical treatment or who have never tried medical treatment but are trying to conceive, so they are not medical candidates, or individuals who genuinely want a diagnosis for surgical management—sometimes even before first-line medical treatment.

Dr. Brown: Your examination sometimes also dictates your approach. A patient may never have had a laparoscopy or hormone therapy, but if you find uterosacral ligament nodularity, extreme pain on examination, and suspicious findings on ultrasound or otherwise, a diagnostic laparoscopy may be warranted to confirm the diagnosis.

Endometrioma management

Dr. Advincula: Let's jump ahead. You have decided to proceed with laparoscopy and you encounter an endometrioma. What is your management strategy, particularly in a fertility-desiring patient?

Dr. Hur: Even if a woman has not undergone first-line medical treatment, if she is trying to conceive or presents with infertility, it's a different balancing act for approaching the patient. When a woman presents, either with an ultrasound finding or an intraoperative finding of an endometrioma, I am a strong advocate of treating symptomatic disease, which means complete cyst excision. Good clinical data suggest that reproductive outcomes are improved for spontaneous pregnancy rates when you excise an endometrioma.[3-6]

Dr. Advincula: What are the risks of excision of an endometrioma cyst that patients need to know about?

Dr. Brown: Current standard of care is cystectomy, stripping the cyst wall away from the ovarian cortex. There is some concern that the stripping process, depending on how long the endometrioma has been present within the ovary, can cause some destruction to the underlying oocytes and perhaps impact that ovary's ability to produce viable eggs.

Some studies, from France in particular, have investigated different energy sources, such as plasma energy, that make it possible to remove part of the cyst and then use the plasma energy to vaporize the rest of the cyst wall that may be lying on the cortex. Researchers looked at anti-Müllerian hormone levels, and there does seem to be a difference in terms of how you remove the cyst.[7-9] This energy source is not available to everyone; it's similar to laser but does not have as much penetration. Standard of care is still ovarian stripping.

The conversation with the patient—if she is already infertile and this cyst is a problem—

TABLE US Food and Drug Administration–approved drug classes for endometriosis treatment

Class	Drug	Adverse effects
Androgenic steroids	• Danazol	Hair loss, weight gain, acne, hirsutism
Estrogen-progestin combinations	• Monophasic estrogen-progestin	Breakthrough bleeding, breast tenderness, nausea, headaches, mood changes
Gonadotropin-releasing hormone agonists	• Goserelin • Leuprolide depot • Nafarelin	Decreased bone density, atrophic vaginitis, hot flashes, headache, joint pain
Progestins	• Depo-Provera • Norethindrone acetate	Acne, weight gain, mood changes, headache, breakthrough bleeding, breast tenderness, lipid abnormalities (norethindrone)

Source: Falcone T, Flyckt R. Clinical management of endometriosis [published online ahead of print February 5, 2018]. Obstet Gynecol. doi:10.1097/AOG.0000000000002469.

would be that it likely needs to be removed. There is a chance that she may need assisted reproduction; she might not be able to get pregnant on her own due either to the presence of the endometrioma or to the surgical process of removing it and stripping.

Dr. Advincula: How soon after surgery can a patient start to pursue trying to get pregnant?

Dr. Hur: I think there is no time restraint outside of recovery. As long as the patient has a routine postoperative course, she can try to conceive, spontaneously or with assisted reproduction. Some data suggest, however, that ovarian reserve is diminished immediately after surgery.[10–12] If you look at the spontaneous clinical pregnancy outcomes, they are comparable 3 to 6 months postsurgery.[4,12–14]

Dr. Brown: I agree. Time is of the essence with a lot of patients, many of whom present after age 35.

Dr. Hur: It's also important to highlight that there are 2 presentations with endometrioma: the symptomatic patient and the asymptomatic patient. In the asymptomatic patient, her age, reproductive goals, and the bilaterality (whether it is present on both sides or on one side) of the endometrioma are important in deciding on a patient-centered surgical plan. For someone with a smaller cyst, unilateral presentation, and maybe older age at presentation, it may or may not impact assisted reproductive outcomes.

If the patient is not symptomatic and she is older with bilateral endometriomas less than 4 cm, some data suggest that patient might be better served in a conservative fashion.[6,15–17] Then, once she is done with assisted reproduction, we might be more aggressive surgically by treating the finding that would not resolve spontaneously without surgical management. It is important to highlight that endometriomas do not resolve on their own; they require surgical management.

Endometriosis management for the patient not seeking fertility

Dr. Advincula: Let's now consider a patient on whom you have performed laparoscopy not only to diagnose and confirm the evidence of endometriosis but also to treat endometriosis, an endometrioma, and potentially deeply infiltrative disease. But this person is not trying to get pregnant. Postoperatively, what is your approach?

Dr. Brown: Suppressive therapy for this patient could be first-line or second-line therapy, such as a Lupron Depot or Depo-Provera. We keep the patient on suppressive therapy (whatever treatments work for her), until she's ready to get pregnant; then we take her off. Hopefully she gets pregnant. After she delivers, we reinitiate suppressive therapy. I will follow these women throughout their reproductive cycle, and I think having a team of physicians who are all on the same page can help this patient manage her disease through her reproductive years.

"If the patient is not symptomatic and she is older with bilateral endometriomas less than 4 cm, some data suggest that patient might be better served in a conservative fashion."

—Hye-Chun Hur, MD, MPH

Surgical technique: Excision versus ablation

Hye-Chun Hur, MD, MPH: I am a strong advocate of excision of endometriosis. I believe that it's essential to excise for 2 very important reasons. One reason is for diagnosis. Accurately diagnosing endometriosis through visualization alone is poor, even among gynecologic surgeons. It is very important to have an accurate diagnosis of endometriosis, since the diagnosis will then dictate the treatment for the rest of a patient's reproductive life.

The second reason that excision is essential is because you just do not know how much disease there is "behind the scenes." When you start to excise, you begin to appreciate the depth of the disease, and often fibrosis or inflammation is present even behind the endometriosis implant that is visualized.

Douglas N. Brown, MD: I approach endometriosis in the same way that an oncologist would approach cancer. I call it cytoreduction—reducing the disease. There is this iceberg phenomenon, where the tip of the iceberg is seen in the water, but you have no idea how deep it actually goes. That is very much deep, infiltrative endometriosis. Performing an ablation on the top does almost nothing for the patient and may actually complicate the situation by causing scar tissue. If a patient has symptoms, I firmly believe that you must resect the disease, whether it is on the peritoneum, bladder, bowel, or near the ureter. Now, these are radical surgeries, and not every patient should have a radical surgery. It is very much based on the patient's pain complaints and issues at that time, but excision of endometriosis really, in my opinion, should be the standard of care.

Risks of excision of endometriosis

Dr. Brown: The risks of disease excision depend on whether a patient has ureteral disease, bladder disease, or bowel disease, suggested through a preoperative or another operative report or imaging. If this is the case, we have a preoperative discussion with the patient about, "To what extent do you want me to go to remove the disease from your pelvis? If I remove it from your peritoneum and your bladder, there is the chance that you'll have to go home with a Foley catheter for a few days. If the bowel is involved, do you want me to try to resect the disease or shave it off the bowel? If we get into a problem, are you okay with me resecting that bowel?" These are the issues that we have to discuss, because there are potential complications, although known.

Dr. Hur: If a patient presented warranting surgical management once, and she is not menopausal, the likelihood that disease will recur is quite high. Understanding the nature and the pathology of the disease, hormonal suppression would be warranted. Suppression is not just for between pregnancies, it's until the patient reaches natural menopause. It's also in the hopes of suppressing the disease so she does not need recurrent surgeries.

We typically do not operate unless patients have recurrence of symptoms that no longer respond to medical therapy. Our hope is to buy them more time closer to the age of natural menopause so that medical repercussions do not result in hysterectomy and ovary removal, which have other nongynecologic manifestations, including negative impact on bone and cardiac health.

The role of the LNG-IUD

Dr. Advincula: Something that often comes up is the role of a levonorgestrel-releasing intrauterine device (LNG-IUD) as one therapy option, either preoperatively or postoperatively. What is your perspective?

Dr. Hur: I reserve the LNG-IUD as a second-line therapy for patients, predominantly because it allows direct delivery of the medication to the womb (rather than systemic exposure of the medication). For patients who experience adverse effects due to systemic exposure to first-line treatments, it might be a great option. However, I do not believe that it consistently suppresses the ovaries, which we understand feeds the pathology of the hormonal stimulation, and so typically I will reserve it as a second-line treatment.

Dr. Brown: I utilize the LNG-IUD in a similar fashion. I may have patients who have had a diagnostic laparoscopy somewhere else and were referred to me because they now have known stage 3 or 4 endometriosis without endometriomas. Those patients, if they are going to need suppressive therapy after surgery and are not ready to get pregnant, do very well with the LNG-IUD, and I will place it during surgery under anesthesia. If a patient has endometriomas seen at the time of surgery, we could still place an LNG-IUD at the time of surgery. We may need to add on an additional medication, however, like another oral progesterone. I do have patients that use both an IUD and either combined oral contraceptive pills and/or oral progestins. Those patients usually have complicated cases with very deep infiltrative disease.

Managing endometriosis involving the bowel

Dr. Advincula: Patients often are quite concerned when the words "endometriosis" and "bowel" come together. How do you manage disease that involves the bowel?

Dr. Hur: A lot of patients with endometriosis

have what I call neighboring disease—it's not limited just to the pelvis, but it involves the neighboring organs including the bowel and bladder. Patients can present with symptoms related to those adjacent organs. However, not all disease involving the bowel or bladder manifests with symptoms, and patients with symptoms may not have visible disease.

Typically, when a patient presents with symptoms of bowel involvement, where the bowel lumen is narrowed to more than 50% and/or she has functional manifestations (signs of obstruction that result in abnormal bowel function), we have serious conversations about a bowel resection. If she has full-thickness disease without significant bowel dysfunction—other than blood in her stool—sometimes we talk about more conservative treatment because of the long-term manifestations that a bowel resection could have.

Dr. Brown: I agree completely. It is important to have a good relationship with our colorectal surgeons. If I suspect that the patient has narrowing of the lumen of the large bowel or she actually has symptoms such as bloody diarrhea during menstruation—which is suggestive of deep, infiltrative and penetrative disease—I will often order a colonoscopy ahead of time to get confirmed biopsies. Then the patient discussion occurs with our colorectal surgeon, who operates with me jointly if we decide to proceed with a bowel resection. It's important to have subspecialty colleagues involved in this care, because a low anterior resection is a very big surgery and there can be down-the-stream complications.

The importance of multidisciplinary care

Dr. Advincula: What are your perspectives on a multidisciplinary or interdisciplinary approach to the patient with endometriosis?

Dr. Brown: As I previously mentioned, it is important to develop a good relationship with colorectal surgery/urology. In addition, behavioral therapists may be involved in the care of patients with endometriosis, for a number of reasons. The disease process is fluid. It will change during the patient's reproductive years, and you need to manage it accordingly based on her symptoms. Sometimes the diagnosis is not made for 5 to 10 years, and that can lead to other issues: depression, fibromyalgia, or irritable bowel syndrome.

The patient may have multiple issues plus endometriosis. I think having specialists such as gastroenterologists and behavioral therapists on board, as well as colorectal and urological surgeons who can perform these complex surgeries, is very beneficial to the patient. That way, she benefits from the team's focus and is cared for from start to finish.

Dr. Hur: I like to call the abdomen a studio. It does not have separate compartments for each organ system. It's one big room, and often the neighboring organs are involved, including the bowel and bladder. I think Dr. Brown's observation—the multidisciplinary approach to a patient's comprehensive care—is critical. Like any surgery, preoperative planning and preoperative assessment are essential, and these steps should include the patient. The discussion should cover not only the surgical outcomes that the surgeons expect, but also what the patient expects to be improved. For example, for patients with extensive disease and bowel involvement, a bowel resection is not always the right approach because it can have potential long-term sequelae. Balancing the

"Having specialists such as gastroenterologists and behavioral therapists on board, as well as colorectal and urological surgeons who can perform these complex surgeries, is very beneficial to the patient. That way, she benefits from the team's focus and is cared for from start to finish."

—Douglas N. Brown, MD

risks associated with surgery with the long-term benefits is an important part of the discussion.

Dr. Advincula: Those are both excellent perspectives. Endometriosis is a very complicated disease state, does require a multidisciplinary approach to management, and there are implications and strategies that involve both the medical approach to management and the surgical approach. ●

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OBG MANAGEMENT

ACOG app and applets: Tools to augment your practice

Useful information at your fingertips

Katherine T. Chen, MD, MPH

The American College of Obstetricians and Gynecologists (ACOG) is a nonprofit organization of women's health care physicians advocating the highest standards of practice, continuing member education, and public awareness of women's health care issues.[1] The organization has long recognized the impact that social media and mobile technology would have for itself as well as its membership. ACOG published a Social Media Guide in 2012, featuring a section on how to use apps in ObGyn practice and provided a list of apps for ObGyns and their patients.[2]

ACOG introduced its own app 4 years ago and has since updated the app several times, most recently on December 6, 2017. The ACOG app has a useful search function, a home button, and a place for users to email feedback (**TABLE 1**, page 42). The app most importantly contains several applets (small applications designed to perform a specific function within the main application). These applets encompass 3 types of apps for health care providers: clinical decision-making apps (Practice Bulletins, Committee Opinions, an Estimated Due Date Calculator that was featured in a prior review,[3] Indicated Delivery, and Immunize) (**TABLE 2**, page 42), reference and information gathering apps (Today's Headlines), and member support apps (ACOG Contacts, Careers, Annual Meeting, Districts, Council on Resident Education in Obstetrics and Gynecology [CREOG], and Website).[4]

This review will focus on the main ACOG app, which is evaluated by a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature use, and important special features).[5] In addition, the clinical decision-making applets will be highlighted in a second table. I commend ACOG for developing these useful tools to augment their members' practices. Of note, for the Practice Bulletins and Indicated Delivery applets, users will need to input their ACOG log-in access information. ●

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The author reports receiving royalties from UpToDate, Inc.

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Review of ACOG app and applets

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TABLE 1 The ACOG app

App	App comprehensiveness	Price	Platform	Literature used	Important special features
ACOG iTunes: https://itunes.apple.com/us/app/acog/id616323665?mt=8 Google Play: https://play.google.com/store/apps/details?id=vspringboard.acog.activity	• Clinical decision-making (clinical decision support systems, clinical treatment guidelines, medical calculators) • Communication and consulting (e-mail) • Reference and information gathering (medical news) • Continuing medical education	Free (a few applets require ACOG log-in)	iTunes and Google Play store	Practice bulletins, committee opinions, and other primary sources	See specific applet descriptions in Table 2

TABLE 2 The ACOG applets

Applet	App type	ACOG log-in required	Literature used	Important special features
Practice Bulletins	Clinical decision-making (clinical treatment guidelines)	Yes	Primary sources	Updates on techniques and clinical management issues
Committee Opinions	Clinical decision-making (clinical treatment guidelines)	No	Primary sources	ACOG committee's assessment of emerging issues in ObGyn practice
EDD Calculator	Clinical decision-making (medical calculators)	No	ACOG Committee Opinion No. 700	• Uses data from last menstrual period and first accurate ultrasound to determine estimated due date (EDD) • Determines both estimated gestational age (EGA) for a target date and target date for a gestational age
Indicated Delivery	Clinical decision-making (clinical decision support systems) Communication and consulting (e-mail)	Yes	None	• Provides members with suggestions related to the timing of delivery based on selected conditions, the patient's EDD/EGA, and ACOG's clinical guidance • Allows members to e-mail or print results for use in counseling patients and or document in patient's record
Immunize	Clinical decision-making (clinical treatment guidelines)	No	National organizations	Interactive tool that provides immunization best practices / recommendations / algorithms

A Supplement to OBG MANAGEMENT

Modern Day Laboring

FEATURING:

Induction of Labor for Low-Risk Women: Is 39 the New 41?

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Mount Sinai Hospital
University of Toronto
Toronto, Canada

Errol R. Norwitz, MD, PhD, MBA
Tufts Medical Centre and Tufts University School of Medicine
Boston, Massachusetts

Cervical Ripening in Alternative Settings: Balancing Logistics and Patient Care

Julian N. Robinson, MD
Brigham and Women's Hospital
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Sarah E. Little, MD
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Boston, Massachusetts

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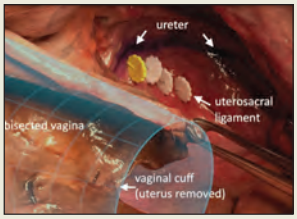
OBG MANAGEMENT

Surgical anatomy and steps of the uterosacral ligament colpopexy

LAUREN N. SIFF, MD; KARL JALLAD, MD; LISA C. HICKMAN, MD; AND MARK D. WALTERS, MD



In this video, the authors illustrate the surgical anatomy of the uterosacral ligament colpopexy. They present images from both cadaveric dissection and live surgery to offer key steps of the procedure from several angles and perspectives. The techniques highlighted include locating and protecting the ureter and rectum, identifying the uterosacral ligament, placing and anchoring the sutures, and elevating the vaginal cuff.

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◀ Use this QR code* to view the video at **mdedge.com/obgmanagement**

*Free QR readers are available for smartphones at the iPhone App Store, Android Market, and BlackBerry App World.

PRODUCT Update

PRENATAL SCREENING FOR SINGLE-GENE DISORDERS

Vistara®, a non-invasive prenatal test (NIPT) from **Natera, Inc**, screens for single-gene disorders after 9 weeks' gestation. Complementing the **Panorama**® NIPT, **Vistara** tests for major anatomic abnormalities and chromosome imbalances that have a combined incidence rate of 1 in 600 (higher than Down syndrome). These mutations can cause severe conditions affecting skeletal, cardiac, and neurologic systems, such as Noonan syndrome, osteogenesis imperfecta, craniosynostosis syndromes, achondroplasia, and Rett syndrome. Standard NIPT commonly cannot detect these *de novo* (not inherited) mutations. Ultrasound exams may either completely miss the disorders or identify nonspecific findings later in pregnancy.

Natera says that **Vistara** has a combined analytical sensitivity of >99% and a combined analytical specificity of >99% in validation studies.

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

ELECTROSTATIC SURGICAL SMOKE REMOVAL

The **Ultravision**™ **Trocar device** from **Alesi Surgical Technologies** uses a low-energy electrostatic charge to eliminate the surgical smoke generated by cutting instruments during laparoscopic surgery. Electrostatic precipitation accelerates the natural process of sedimentation; **Ultravision** creates negatively charged gas ions that draw water vapor and particulate matter away from the surgical site toward "positive" patient tissue.

Alesi says that bench studies comparing **Ultravision** with a vacuum-system when using monopolar, bipolar, and ultrasonic instruments show that its device is faster and more efficient than smoke evacuation. When switched on before cutting, **Ultravision** precipitates 99% of particles within 30 seconds. After 1 minute of continuous use, **Ultravision** precipitates 99.9% of particles, independent of particle size, from 7 nm to 10 µm. Smoke evacuation removes 30.2% of particles after 1 minute, according to **Alesi**.

FOR MORE INFORMATION, VISIT:
http://www.alesi-surgical.com

PRESSURE-SENSING TECHNOLOGY FOR EPIDURALS

The **CompuFlo**® **Epidural** from **Milestone Scientific** uses pressure-sensing technology to identify the epidural space, and provides a computer-controlled drug delivery system.

Knowing the precise needle location during an epidural injection procedure provides a measure of safety not available to physicians who use conventional syringes. **Milestone** says that its **CompuFlo Epidural** allows anesthesiologists to use both hands to advance and direct the needle, and to confirm the epidural space with 99% accuracy on the first attempt.

CompuFlo Epidural differentiates tissue types for the medical professional via visual and audio feedback, leading to precise location guidance as the needle advances toward the intended area. It also allows for controlled needle exit pressure, precise flow rate and drug volumes, and patient treatment documentation.

FOR MORE INFORMATION, VISIT:
https://www.milestonescientific.com/products/compuflo-epidural

OBGYN ULTRASOUND INNOVATIONS

Philips recently announced enhancements to its EPIQ 7 and 5 and Affiniti 70 ultrasound systems. According to **Philips**, the **eL18-4 transducer** provides high-detail resolution and image uniformity with penetration for enhanced diagnostic quality in 1st- and 2nd-trimester obstetric exams. **aBiometry Assist**AI, with anatomical intelligence of fetal anatomy, streamlines fetal measurement by preplacing measurement cursors on selected structures. The new **TouchVue** control-panel interface on **TrueVue** allows practitioners to interact with finger gestures and to direct 3D-volume rotation and internal light-source position. The 2D **Tilt** feature offered on the 3D9-v3 transducer provides lateral scanning of anatomic structures that are off-axis without having to manually angle the transducer.

These new features complement the existing suite of **Philips** ObGyn ultrasound visualization tools: **TrueVue**, **GlassVue**, **aReveal**AI, and **MaxVue**.

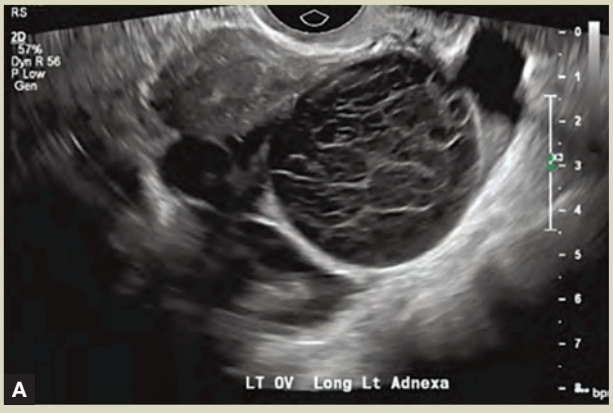
FOR MORE INFORMATION, VISIT:
https://www.usa.philips.com/healthcare/resources/feature-detail/ultrasound-truevue-imaging

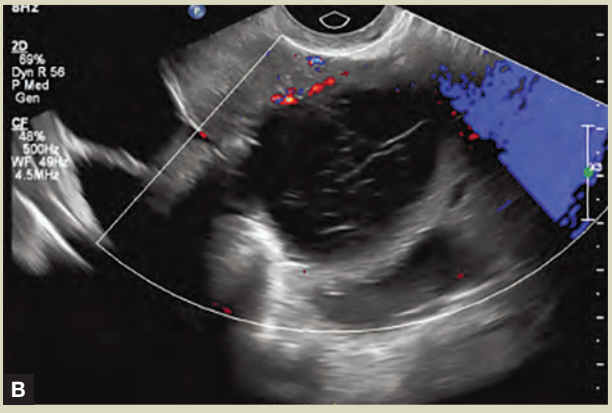
2-week left-sided pelvic pain

Devaraju Kanmaniraja, MD, and Andrew M. Kaunitz, MD

CASE

A 37-year-old woman presents to the emergency department reporting left-sided pelvic pain for 2 weeks duration. She has a negative urine pregnancy test. Pelvic ultrasonography of the left adnexa is performed with gray scale (**A**) and color Doppler images (**B**).





At the time of this writing, Dr. Kanmaniraja was Assistant Professor and Chief, Division of Abdominal Imaging, Department of Radiology, University of Florida College of Medicine–Jacksonville.

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

The authors report no financial relationships relevant to this quiz. This quiz was published online January 23, 2017.

What is the diagnosis based on the sonographic findings?

- Simple ovarian cyst
- Hemorrhagic cyst
- Endometrioma
- Dermoid cyst
- Cystic ovarian neoplasm

Turn the page to see if you are correct.

CONTINUED ON PAGE 46

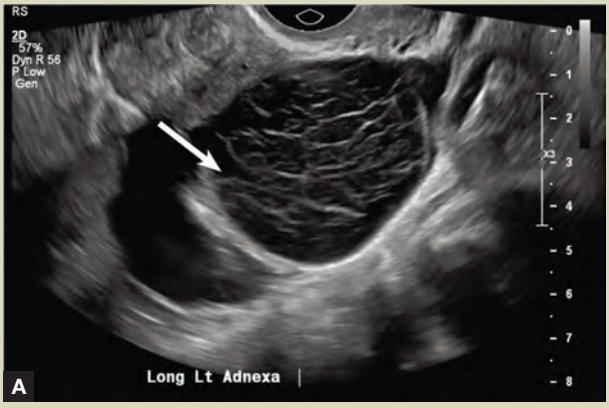
2-week left-sided pelvic pain

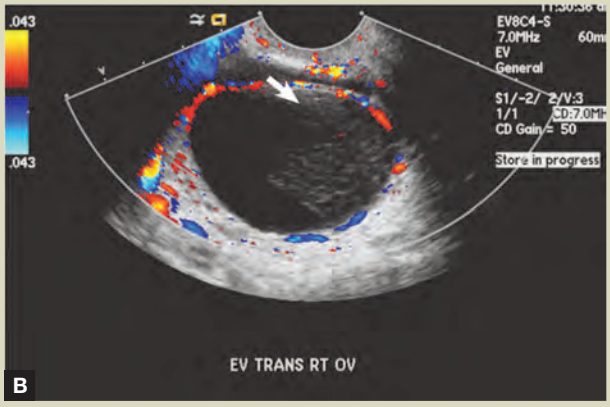
CONTINUED FROM PAGE 45

CORRECT

Hemorrhagic cyst

A hemorrhagic cyst is well-circumscribed and hypoechoic, with posterior acoustic enhancement and a lacy reticular pattern of internal echoes due to fibrin strands. The internal echoes also may be solid appearing with concave margins due to a retractile hemorrhagic clot.[1] The absence of internal vascular flow on color Doppler helps differentiate it from the solid components seen in ovarian neoplasm.



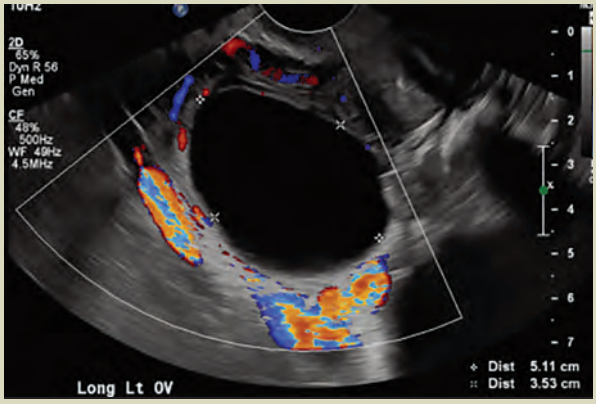


Hemorrhagic cyst. (**A**) Transvaginal pelvic ultrasound of the left ovary demonstrates a well-circumscribed hypoechoic cyst with posterior acoustic enhancement and a lacy reticular pattern of internal echoes (long arrow). (**B**) Transvaginal pelvic ultrasound of the right ovary shows a well-circumscribed hypoechoic cyst with a solid-appearing retractile hemorrhagic clot that has concave margins (short arrow) and no vascular flow on color Doppler.

INCORRECT

Simple ovarian cyst

A simple ovarian cyst is a well-circumscribed, round or oval, anechoic, avascular cyst with posterior acoustic enhancement and thin smooth walls.[1] No septations or solid components will be identified.

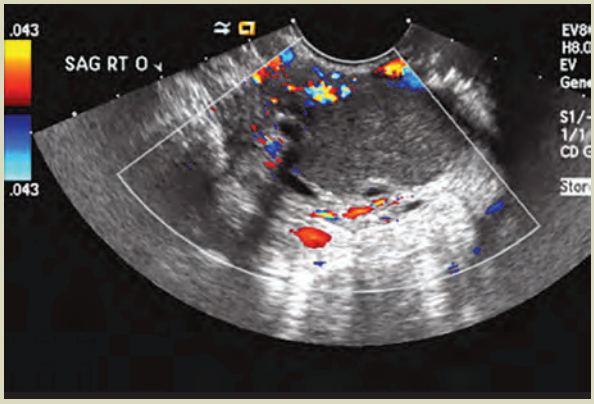


Simple ovarian cyst. Transvaginal pelvic ultrasound of the left ovary demonstrates a well-circumscribed, oval, anechoic, avascular cyst with posterior acoustic enhancement and thin, smooth walls.

INCORRECT

Endometrioma

An endometrioma is a well-circumscribed hypoechoic cyst with homogeneous ground glass or low-level echoes and increased through transmission.[1] It will appear avascular without solid components.

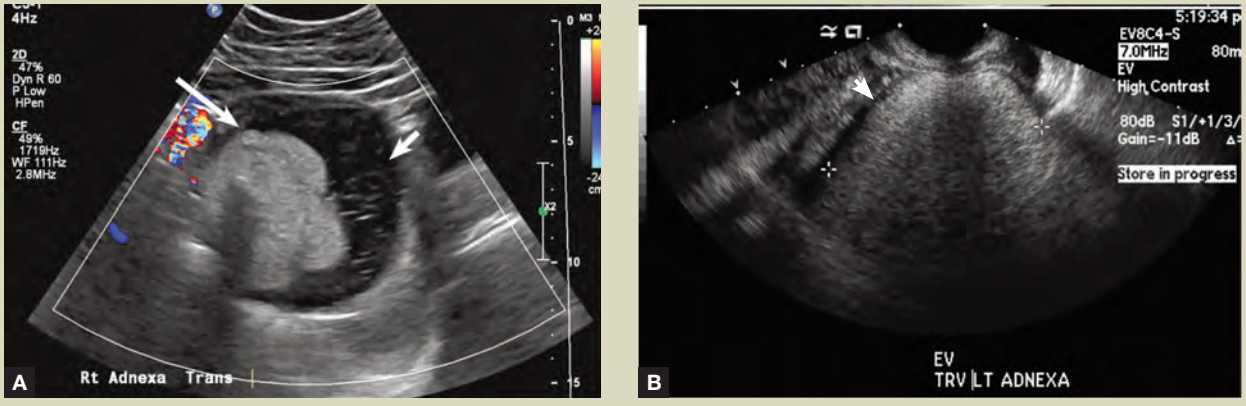


Endometrioma. Transvaginal pelvic ultrasound of the right ovary demonstrates a well-circumscribed, avascular, hypoechoic cyst with homogeneous ground glass or low-level echoes and increased through transmission.

INCORRECT

Dermoid cyst

A dermoid cyst is a common benign ovarian tumor with varying appearances, the most common being a cystic lesion with a focal echogenic nodule protruding into the cyst (Rokitansky nodule).[2] The second most common appearance is a focal or diffuse hyperechoic mass with areas of acoustic shadowing from the sebaceous material and hair (tip-of-the-iceberg sign). A third appearance is a cystic lesion with multiple thin echogenic bands illustrating hair floating within the cyst. No internal vascular flow will be identified.

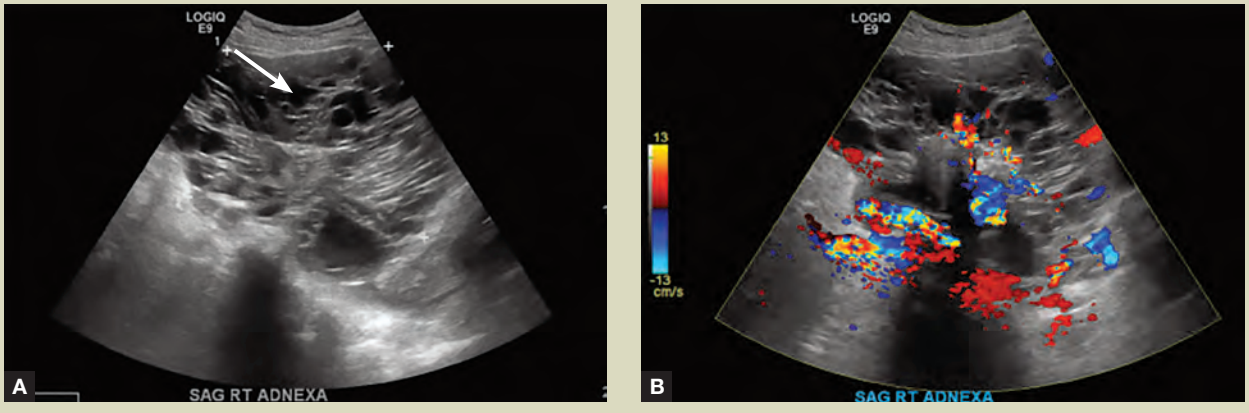


Dermoid cysts. (**A**) Transvaginal pelvic ultrasound of the right adnexa demonstrates a cystic lesion with a focal echogenic nodule protruding into the cyst (Rokitansky nodule) (long arrow) and multiple thin echogenic lines and dots (short arrow). (**B**) Transvaginal pelvic ultrasound of the left adnexa shows a diffuse hyperechoic mass with areas of acoustic shadowing (arrowhead).

INCORRECT

Cystic ovarian neoplasm

A cystic ovarian neoplasm is a large complex mass with both cystic and solid components showing internal vascular flow. These neoplasms usually demonstrate a thick irregular wall, multiple septations, and nodular papillary projections.[3]



Borderline ovarian neoplasm. (**A**) Transvaginal pelvic ultrasound of the right adnexa demonstrates a large complex cystic and solid mass with a thick irregular wall, multiple septations (arrow), and nodular papillary projections. (**B**) The mass shows internal vascular flow on color Doppler images. ●

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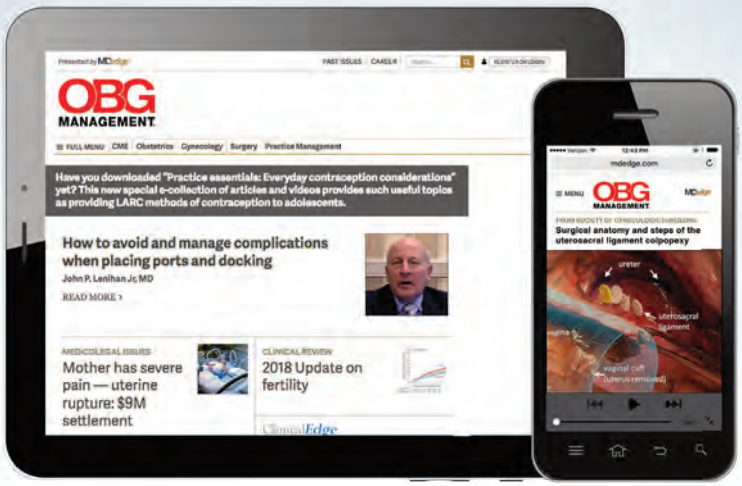

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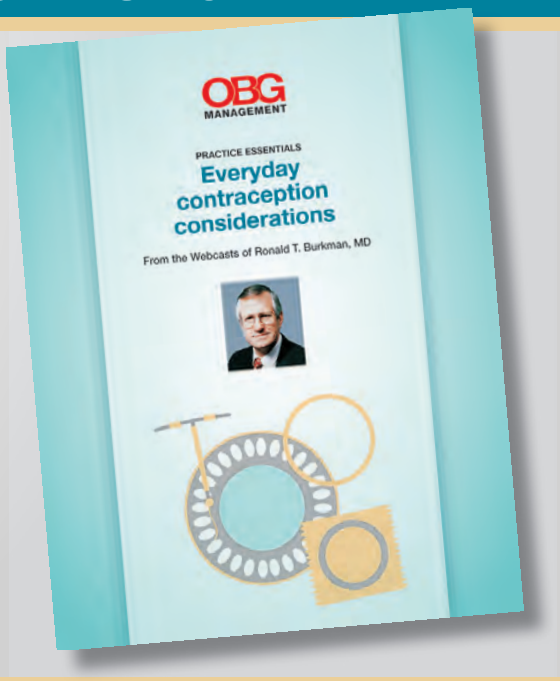

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COMMENT & CONTROVERSY

CONTINUED FROM PAGE 13

days I would order oxycodone plus acetaminophen for 1 to 2 days postoperative cesarean delivery, and only 1 day after normal spontaneous delivery if the patient had a large perineal repair or multiparous involution pain. Otherwise, it was ibuprofen 800 mg, then 400 to 600 mg on discharge home.

Gabrielle Long, CNM
Mohegan Lake, New York

Respect women's postsurgical pain management needs

There is a real disrespect for pain control for women, such as after a cesarean delivery. I would like to see any male have major surgery through a large muscle like the uterus and not need significant pain control options!

Anne V. Hale, MD
El Paso, Texas

Dr. Barbieri responds

I agree with Ms. Long that most postpartum patients, including many who have had a cesarean delivery, can achieve adequate pain control with the use of parenteral and oral nonsteroidal anti-inflammatory drugs (NSAIDs) and oral acetaminophen. Drs. Toler and Hale are concerned that postpartum pain control might be suboptimal if opioids are underprescribed. However, in many developed countries obstetricians do not use opioid pain medicine for postpartum pain management, relying on NSAIDs and acetaminophen. Given the success of this approach, I think we can significantly reduce the use of opioids by postpartum women in the United States by optimizing our use of nonopioid medications.

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NOW AVAILABLE

DEMONSTRATED TO SIGNIFICANTLY DECREASE MODERATE TO SEVERE **DYSPAREUNIA DUE TO MENOPAUSE**[1]

Not actual size.

NON-ESTROGEN BASED, CONVERTS TO ESTROGENS AND ANDROGENS*

Prasterone is a precursor that is locally converted to estrogens and androgens with minimal systemic exposure.[1,2] *The mechanism of action of INTRAROSA is not fully established[1]

ONCE-DAILY TREATMENT

Individually wrapped vaginal inserts with disposable applicators[1]

NO FDA BOXED WARNING[2]

No restrictions on duration of use[2,3]

To order samples and learn more about INTRAROSA, including our patient savings program, visit IntrarosaHCP.com

Indication

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

Important Safety Information

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS Current or Past History of Breast Cancer

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

ADVERSE REACTIONS Clinical Trials Experience

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

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

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

References: 1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2017. **2.** Archer DF, Labrie F, Bouchard C, et al; VVA Prasterone Group. *Menopause*. 2015;22(9):950-963. **3.** Labrie F, Archer DF, Koltun W, et al; VVA Prasterone Research Group. *Menopause*. 2016;23(3):243-256.

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Intrarosa™ Prasterone VAGINAL INSERTS