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OBG MANAGEMENT

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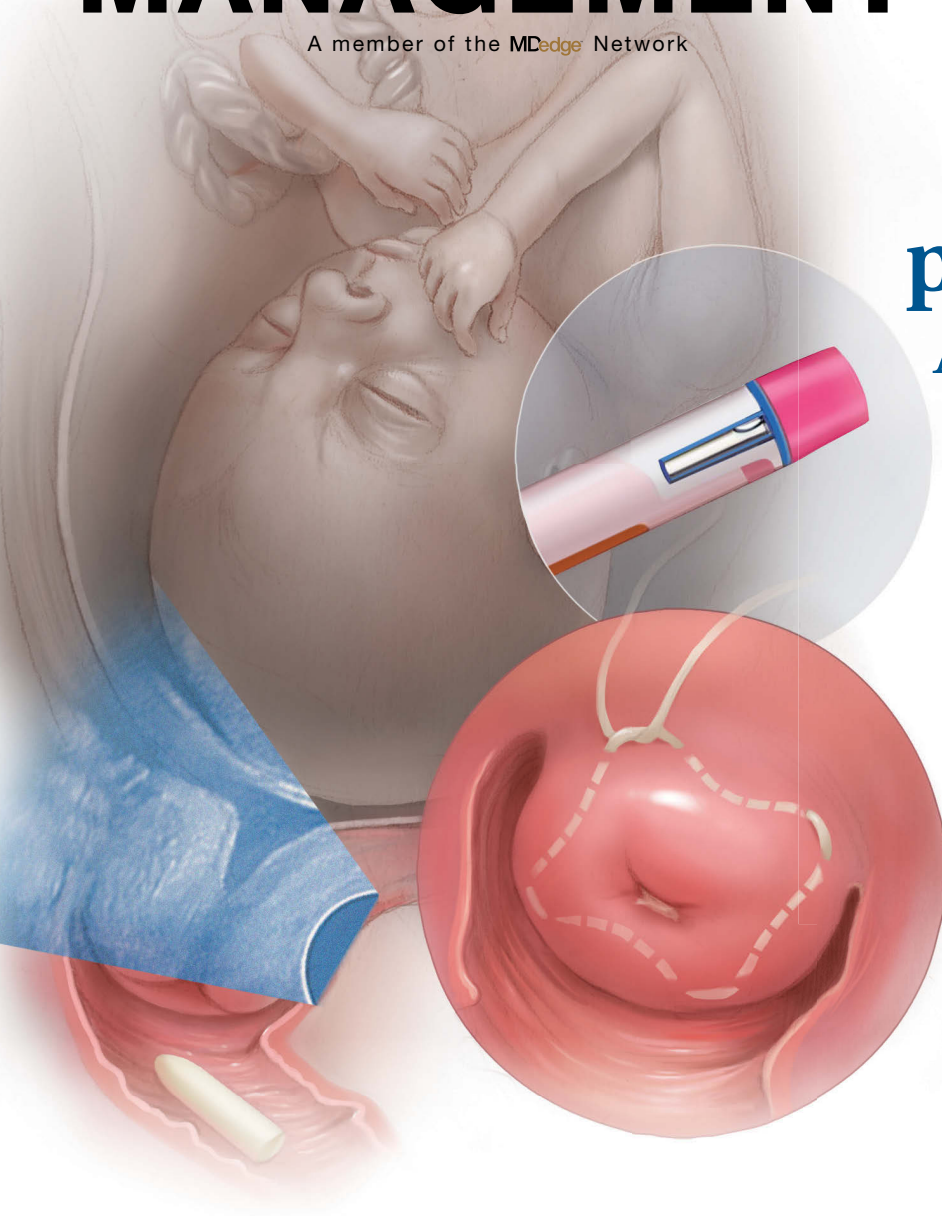
Retained placenta: How long until manual removal?
Robert L. Barbieri, MD

One vs Two Step test for diagnosing GDM

Preventing group B streptococcal disease in newborns



Managing preterm birth

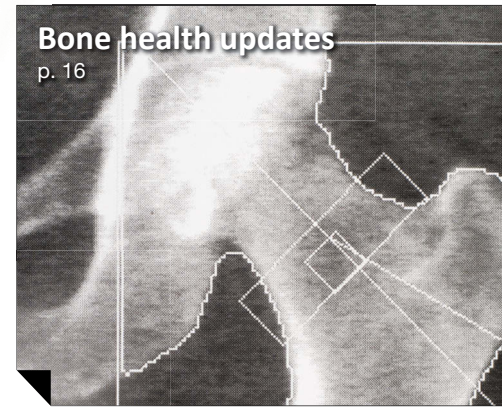
As options appear to be dwindling, what now?

Michael House, MD, and Errol Norwitz, MD, PhD, MBA

PLUS A REPORT FROM THE FIELD

4 experts share preterm birth management strategies

Planned early delivery for preterm preeclampsia?



COLORECTAL CANCER IS THE MOST PREVENTABLE, YET LEAST PREVENTED FORM OF CANCER.[1]

COLOGUARD® IS RECOMMENDED BY ACOG^[2] AND HAS BEEN CLINICALLY SHOWN TO DETECT AND RULE OUT COLORECTAL CANCER.[3]

92%
SENSITIVITY IN DETECTING CRC STAGES I-IV*[3]

87%
SPECIFICITY OVERALL†[3]

99.94%
NEGATIVE PREDICTIVE VALUE
If a patient received a negative Cologuard test result, there was a 99.94% chance that there was no CRC‡[3]

TO HELP DETECT CRC, OFFER COLOGUARD AS A CHOICE TO SCREEN APPROPRIATE WOMEN AS SOON AS THEY ARE ELIGIBLE.

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 45 years or older, who are at typical average risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Cologuard is not for high-risk individuals, including patients with a personal history of colorectal cancer and adenomas; have had a positive result from another colorectal cancer screening method within the last 6 months; have been diagnosed with a condition associated with high risk for colorectal cancer such as IBD, chronic ulcerative colitis, Crohn's disease; or have a family history of colorectal cancer, or certain hereditary syndromes.

Positive Cologuard results should be referred to diagnostic colonoscopy. A negative Cologuard test result does not guarantee absence of cancer or advanced adenoma. Following a negative result, patients should continue participating in a screening program at an interval and with a method appropriate for the individual patient.

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

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

^In the recommendations, Cologuard is referred to as FIT-DNA.

*Cologuard sensitivity, per stage of cancer: I: 90% (n=29); II: 100% (n=21); III: 90% (n=10); IV: 75% (n=4).[3]

†Cologuard specificity: 87% overall specificity, excluding CRC and advanced adenomas, and including all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy. 90% specificity in participants with no lesions biopsied on colonoscopy.[3]

‡Negative predictive value (NPV) is defined as the probability that disease is absent in those with a negative result; it is highly dependent on the prevalence of the disease. NPV was derived from the patient population evaluated in the Imperiale et al publication.[3]

REFERENCES: 1. Itzkowitz SH. Incremental advances in excremental cancer detection tests. *J Natl Cancer Inst.* 2009;101(18):1225-1227. **2.** Well-woman recommendations: ages 40–64 years: laboratory and other tests—ACOG. American College of Obstetricians and Gynecologists website. https://www.acog.org/About-ACOG/ACOG-Departments/Annual-Womens-Health-Care/Well-Woman-Recommendations/Laboratory-Testing-Ages-40-64-Years. Accessed May 22, 2019. **3.** Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;370(14):1287-1297.

EXACT SCIENCES CORPORATION
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cologuard® Rx only

EXACT SCIENCES

#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†

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

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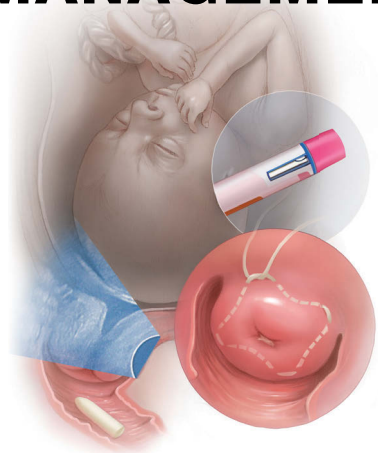
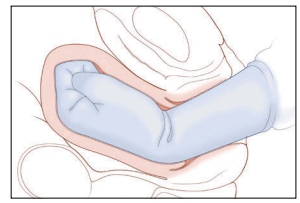
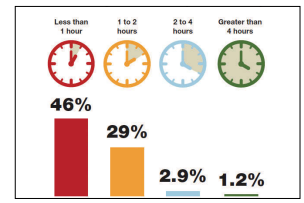




Restoration of uterine anatomy **8**



Antibiotics for GBS **26**

FAST TRACK **FAST TRACK** is a system to enable you as a reader to move quickly through each issue of **OBG MANAGEMENT**, identifying articles or sections of articles to read in depth.

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WEB EXCLUSIVE

OTC hormonal contraception: An important goal in the fight for reproductive justice

ABBY L. SCHULTZ, MD, AND MEGAN L. EVANS, MD, MPH

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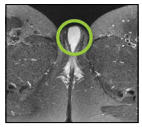

A clitoral cyst of "epidermal" proportions

ANGELA DICARLO-MEACHAM, LCDR, MC, USN; KATHERINE L. DENGLER, MAJ, MC, USA; ANDREA N. SNITCHLER, CDR, MC, USA; AND DANIEL D. GRUBER, COL, MC, USAF

See QR code on page 50

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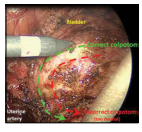

Tips and tricks for laparoscopic colpotomy

NOOR M. ABUALNADI, MD, AND MICHELLE LOUIE, MD

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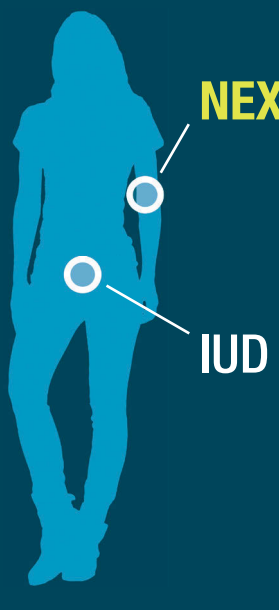

Help your patients understand both of their LARC location options[1]

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

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

US-XPL-00588 05/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

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

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

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

Nexplanon®
(etonogestrel implant) 68mg

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1810r020
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EDITORIAL

Retained placenta after vaginal birth: How long should you wait to manually remove the placenta?

For a woman with a neuraxial anesthetic, 20 minutes post–birth of the newborn may be the best time to diagnose retained placenta and consider manual removal

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Harvard Medical School

You have just safely delivered the baby who is quietly resting on her mother's chest. You begin active management of the third stage of labor, administering oxytocin, performing uterine massage and applying controlled tension on the umbilical cord. There is no evidence of excess postpartum bleeding.

How long will you wait to deliver the placenta?

Active management of the third stage of labor

Most authorities recommend active management of the third stage of labor because active management reduces the risk of maternal hemorrhage >1,000 mL (relative risk [RR], 0.34), postpartum hemoglobin levels < 9 g/dL (RR, 0.50), and maternal blood transfusion (RR, 0.35) compared with expectant management.[1]

The most important component of active management of the third stage of labor is the administration of a uterotonic after delivery of the newborn. In the United States, oxytocin is the uterotonic most often utilized for the active management of the third stage of labor. Authors of a recent randomized clinical trial reported that intravenous oxytocin is superior to intramuscular oxytocin for reducing postpartum blood loss (385 vs 445 mL), the frequency of blood loss greater than 1,000 mL (4.6% vs 8.1%), and the rate of maternal blood transfusion (1.5% vs 4.4%).[2]

In addition to administering oxytocin, the active management of the third stage often involves maneuvers to accelerate placental delivery, including the Crede and Brandt-Andrews maneuvers and controlled tension on the umbilical cord. The Crede maneuver, described in 1853, involves placing a hand on the abdominal wall near the uterine fundus and squeezing the uterine fundus between the thumb and fingers.[3,4]

The Brandt-Andrews maneuver, described in 1933, involves placing a clamp on the umbilical cord close to the vulva.[5] The clamp is used to apply judicious tension on the cord with one hand, while the other hand is placed on the mother's abdomen with the palm and fingers overlying the junction between the uterine corpus and the lower segment. With judicious tension on the cord, the abdominal hand pushes the uterus upward toward the umbilicus. Placental separation is indicated when lengthening of the umbilical cord occurs. The Brandt-Andrews maneuver may be associated with fewer cases of uterine inversion than the Crede maneuver.[5-7]

Of note, umbilical cord traction has not been demonstrated to reduce the need for blood transfusion or the incidence of postpartum hemorrhage (PPH) >1,000 mL, and it is commonly utilized by obstetricians and midwives.[8,9] Hence, in the third stage, the delivering clinician should routinely administer a uterotonic, but use of judicious tension on the cord can be deferred if the woman prefers a noninterventional approach to delivery.

CONTINUED ON PAGE 10

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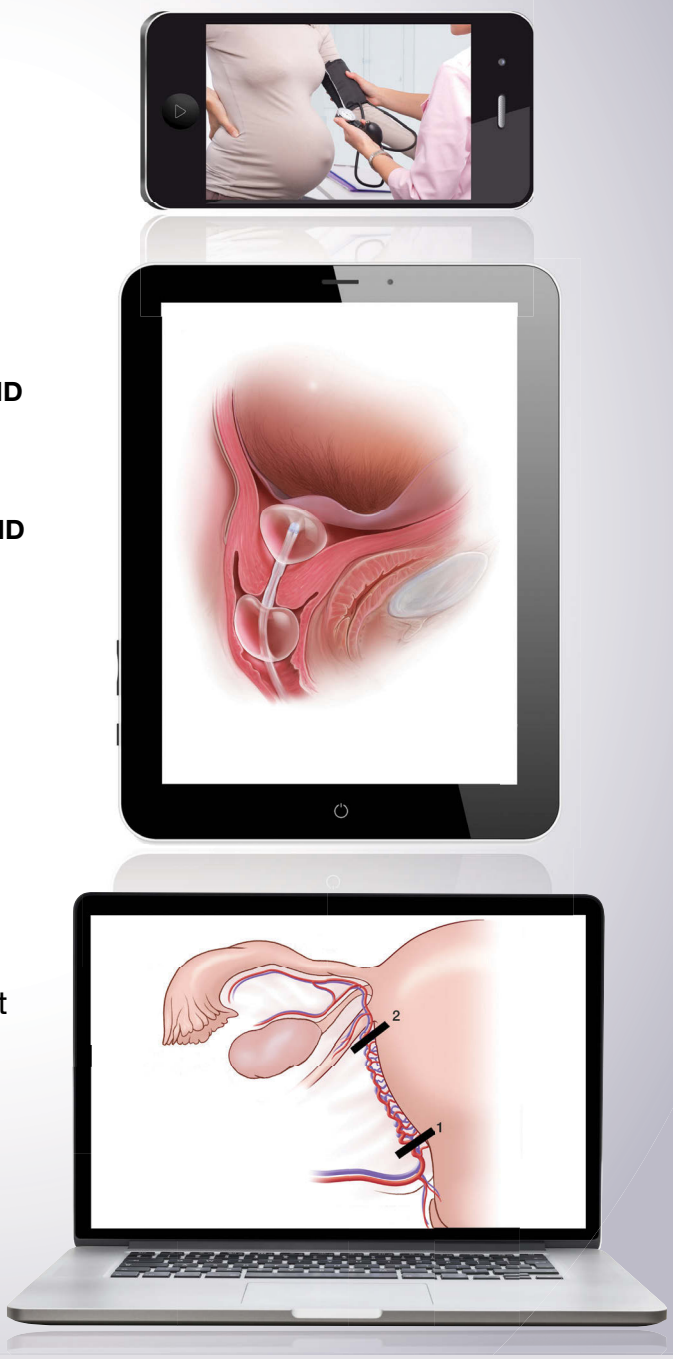

OBG MANAGEMENT

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Beware of placenta accreta spectrum disorder, and be ready to recognize and treat uterine inversion

The retained placenta may prevent the uterine muscle from effectively contracting around penetrating veins and arteries, thereby increasing the risk of postpartum hemorrhage. The placenta that has separated from the uterine wall but is trapped inside the uterine cavity can be removed easily with manual extraction. If the placenta is physiologically adherent to the uterine wall, a gentle sweeping motion with an intrauterine hand usually can separate the placenta from the uterus in preparation for manual extraction. However, if a placenta accreta spectrum disorder is contributing to a retained placenta, it may be difficult to separate the densely adherent portion of the uterus from the uterine wall. In the presence of placenta accreta spectrum disorder, vigorous attempts to remove the placenta may precipitate massive bleeding. In some cases, the acchoucheur/midwife may recognize the presence of a focal accreta and cease attempts to remove the placenta in order to organize the personnel and equipment needed to effectively treat a potential case of placenta accreta. In one study, when a placenta accreta was recognized or suspected, immediately ceasing attempts at manually removing the placenta resulted in better case outcomes than continued attempts to remove the placenta.[1]

Uterine inversion may occur during an attempt to manually remove the placenta. There is universal agreement that once a uterine inversion is recognized it is critically important to immediately restore normal uterine anatomy to avoid massive hemorrhage and maternal shock. The initial management of uterine inversion includes:

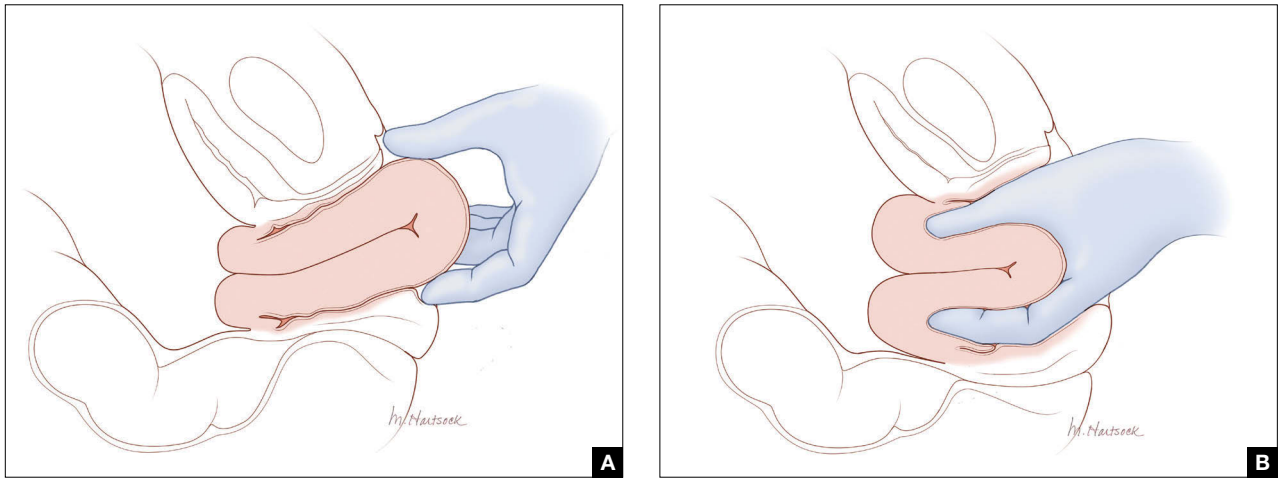

FIGURE 1 Use of the finger tips to guide the uterine wall back to normal anatomy.

Following a vaginal birth, when should the diagnosis of retained placenta be made?

The historic definition of retained placenta is nonexpulsion of the placenta 30 minutes after delivery of the newborn. However, many observational studies report that, when active management of the third stage is utilized, 90%, 95%, and 99% of placentas deliver by 9 minutes, 13 minutes, and 28 minutes, respectively.[10] In addition, many observational studies report that the incidence of PPH increases significantly with longer intervals between birth of the newborn and delivery of the placenta. In one study the rate of blood loss >500 mL was 8.5% when the placenta delivered between 5 and 9 minutes and 35.1% when the placenta delivered ≥30 minutes following birth of the baby.[10] In another observational study, compared with women delivering the placenta < 10 minutes after birth, women delivering the placenta ≥30 minutes after birth had a 3-fold increased risk of PPH.[11] Similar findings have been reported in other studies.[12-14]

Based on the association between a delay in delivery of the placenta and an increased risk of PPH, some authorities recommend that, in term pregnancy, the diagnosis of retained placenta should be made at 20 minutes following birth and consideration should be given to removing the placenta at this time. For women with effective neuraxial anesthesia, manual removal of the placenta 20 minutes following birth may be the best decision for balancing the benefit of preventing PPH with the risk of unnecessary intervention. For women with no anesthesia, delaying manual removal of the placenta to 30 minutes or more following birth may permit more time for the placenta to deliver prior to performing an intervention

ILLUSTRATIONS: MARCIA HARTSOCK FOR OBG MAMAGEMENT

- stopping oxytocin infusion
- initiating high volume fluid resuscitation
- considering a dose of a uterine relaxant, such as nitroglycerin or terbutaline
- preparing for blood product replacement.

In my experience, when uterine inversion is immediately recognized and successfully treated, blood product replacement is not usually necessary. However, if uterine inversion has not been immediately recognized or treated, massive hemorrhage and shock may occur.

Two approaches to the vaginal restoration of uterine anatomy involve using the tips of the fingers and palm of the hand to guide the wall of the uterus back to its normal position (**FIGURE 1**) or to forcefully use a fist to force the uterine wall back to its normal position (**FIGURE 2**). If these maneuvers are unsuccessful, a laparotomy may be necessary.

At laparotomy, the Huntington or Haultain procedures may help restore normal uterine anatomy. The Huntington procedure involves using clamps to apply symmetrical tension to the left and right round ligaments and/or uterine serosa to sequentially tease the uterus back to normal anatomy.[2,3] The Haultain procedure involves a vertical incision on the posterior wall of the uterus to release the uterine constriction ring that is preventing the return of the uterine fundus to its normal position (**FIGURE 3**).[4,5]

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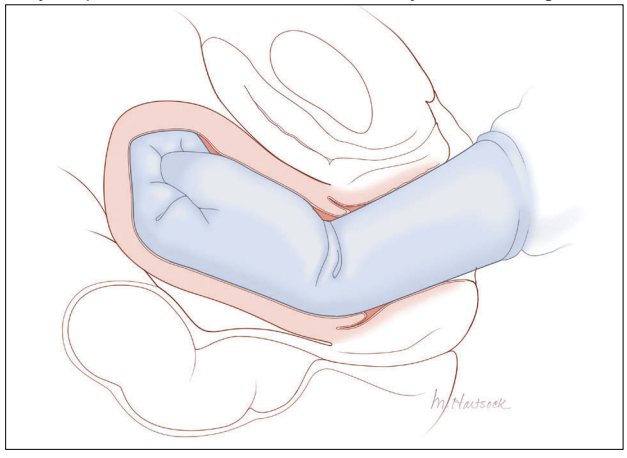

FIGURE 2 Use of the fist to force the uterine wall back to its normal position.

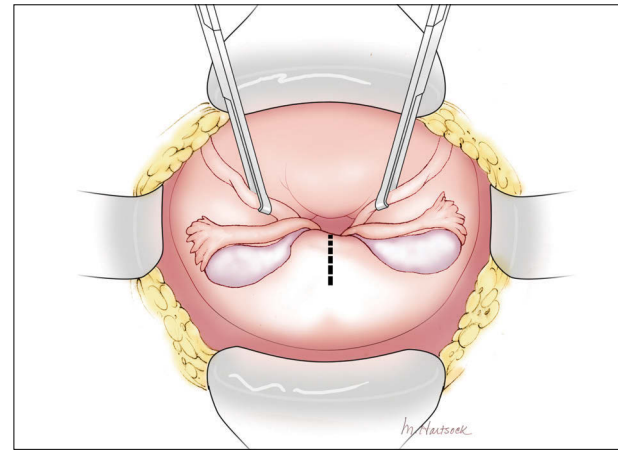

FIGURE 3 The Haultain procedure for correction of inversion of the uterus.

that might cause pain, but the delay increases the risk of PPH.

Manual extraction of the placenta

Prior to performing manual extraction of the placenta, a decision should be made regarding the approach to anesthesia and perioperative antibiotics. Manual extraction of the placenta is performed by placing one hand on the uterine fundus to stabilize the uterus and using the other hand to follow the umbilical cord into the uterine cavity. The intrauterine hand is used to separate the uterine-placental interface with a gentle sweeping motion. The placental mass is grasped and gently teased through the cervix and vagina. Inspection of the placenta to ensure complete removal is necessary.

An alternative to manual extraction of the placenta is the use of Bierer forceps and ultrasound guidance to tease the placenta through the cervical os. This technique involves the following steps[15]:

1. use ultrasound to locate the placenta
2. place a ring forceps on the anterior lip of the cervix
3. introduce the Bierer forcep into the uterus
4. use the forceps to grasp the placenta and pull it toward the vagina
5. stop frequently to re-grasp placental tissue that is deeper in the uterine cavity
6. once the placenta is extracted, examine the placenta to ensure complete removal.

Of note when manual extraction is used to deliver a retained placenta, randomized clinical trials report no benefit for the following interventions:

- perioperative antibiotics[16]
- nitroglycerin to relax the uterus[17]
- ultrasound to detect retained placental tissue.[18]

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Best timing for manual extraction of the placenta

The timing for the diagnosis of retained placenta, and the risks and benefits of manual extraction would be best evaluated in a large, randomized clinical trial. However, based on observational studies, in a term pregnancy, the diagnosis of retained placenta is best made using a 20-minute interval. In women with effective neuraxial anesthesia, consideration should be given to manual removal of the placenta at that time. ●

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

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Do ObGyns think the EMR has improved patient care?

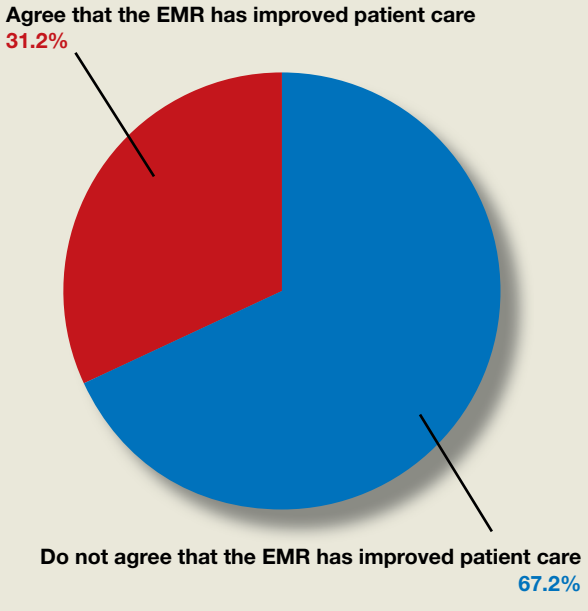
In the roundtable article, "The electronic medical record's role in ObGyn burnout and patient care" (October 2019), Megan L. Evans, MD, MPH; John J. Dougherty, MD, MBA; and Mark B. Woodland, MS, MD, discussed burnout's connection with the electronic medical record (EMR) and solutions implemented at their institutions to help cope with the problem. They highlighted changes they felt their EMR systems needed to undergo. In addition, they noted as a whole that the EMR has not improved patient care.

OBG MANAGEMENT polled readers to see their thoughts on this question: "Do you think that the EMR has improved patient care?"

Poll results

A total of 123 readers cast their vote:

- **67.2% (84 readers)** said no
- **31.2% (39 readers)** said yes



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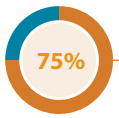
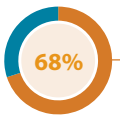
About **ONE** in **TWO** sexually active people will acquire an STI by **AGE 25.**

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



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



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

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

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

Universal screening may help to:[2]

- Decrease STI prevalence
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- Reduce health care cost

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Does planned early delivery make sense in women with preterm preeclampsia?

Maybe. The choice of early delivery reduces the risk of adverse outcomes in the mother, with an increased chance of the neonate's admission to the NICU. The decision has to be individualized.

Chappell LC, Brocklehurst P, Green ME, et al; PHOENIX Study Group. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. Lancet. 2019;394:1181-1190.

EXPERT COMMENTARY
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FAST TRACK

The proportion of women with the maternal co-primary outcome was significantly lower in the planned delivery group compared with the expectant management group (65% vs 75%)

Preeclampsia is a common hypertensive disorder of pregnancy. Among women who develop the disease at late preterm gestation, the question remains, "What is the optimal timing for delivery?" The American College of Obstetricians and Gynecologists (ACOG) categorizes preeclampsia as "with and without severe features."[1] Delivery is recommended for women with preeclampsia with severe features at or beyond 34 weeks' gestation, and for women with preeclampsia without severe features at or beyond 37 weeks' gestation.[1] For patients with fetal growth restriction and preeclampsia, ACOG also recommends delivery between 34 and 37 weeks' gestation.

Details of the study

Chappell and colleagues conducted a randomized controlled trial among women with singleton or dichorionic diamniotic twin pregnancy between 34 and 36.6 weeks' gestation. Women were assigned to either planned delivery within 48 hours of randomization or expectant management until 37 weeks or earlier with clinical deterioration.

Among the 901 women included in the study, 450 were allocated to planned delivery and 451 to expectant management.

Study outcomes. The co-primary short-term maternal outcome was a composite of maternal morbidity with the addition of recorded systolic blood pressure of at least 160 mm Hg postrandomization (on any occasion). The co-primary short-term perinatal outcome was a composite of neonatal deaths within 7 days of delivery and perinatal deaths or neonatal unit admissions.

Participant details. At baseline, the average gestational age at randomization was 35.6 weeks, with equal distribution through the 3 weeks (34 through 36 weeks). About 37% of the women had severe hypertension (≥ 160 mm Hg) in the previous 48 hours prior to randomization, and approximately 22% had fetal growth restriction. The authors did not categorize the women based on severe features of preeclampsia.

Results. The investigators found that the proportion of women with the maternal co-primary outcome was significantly lower in the planned delivery group compared with the expectant management group (65% vs 75%), and the proportion of infants with the perinatal co-primary outcome was significantly higher in the planned delivery group

The author reports no financial relationships relevant to this article.

compared with the expectant management group (42% vs 34%). The fact that early delivery led to more neonatal unit admissions for the infant, principally for a listed indication of prematurity and without an excess of respiratory or other morbidity, intensity of care, or length of stay, is very reassuring.

Study strengths and limitations

This is the largest study of women in this group allocated, randomized, and multicenter investigation addressing a very important clinical question. The patient population was mostly white, with only 13% black women, and had an average body mass index of 29 kg/m^2 (which is low compared with many practices in the United States). The average difference between the 2 study groups was the additional prolongation of pregnancy from enrollment to delivery of only 3 days, which may not be clinically relevant. More than half of the women in the expectant management group had medically indicated delivery before 37 weeks' gestation.

A limitation of this study is that all women with preeclampsia were considered the same—that is, no distinction was made between severe and nonsevere preeclampsia, and a significant proportion of women had severe hypertension at enrollment, which would make them ineligible for expectant management anyway.

The maternal composite outcome was driven mostly by severe hypertension and progression to severe preeclampsia (likely driven by severe hypertension). All other maternal outcomes were very rare or did not happen; however, the incidence of delivery indications for various preeclampsia-related complications was higher in the expectant management group.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In the United States, preeclampsia is categorized as severe or nonsevere, and gestational age at delivery depends on the type of preeclampsia. Clinicians should discuss expectant management after 34 weeks with patients who have preeclampsia without severe features, noting that this may decrease the chances for adverse maternal outcomes (mostly severe hypertension) at the cost of neonatal intensive care unit admission, which may depend on local practices. Attention also should be paid to particular patient populations (such as obese and African American women) who are at higher risk for developing adverse maternal outcomes. This may be particularly relevant in a smaller hospital setting in which patient follow-up may not be universal or access to a maternal-fetal medicine specialist may not be available to discuss management plans.

My personal take: I work in a large tertiary medical center. I worry about added prematurity, especially among women with superimposed preeclampsia where the diagnosis may be unclear. In my practice, we monitor patients with preeclampsia very closely, and with any signs of severe features we deliver them after 34 weeks. We follow ACOG guidelines for managing preeclampsia based on severity of disease and gestational age. I am not planning to immediately change my practice based on this study by Chappell and colleagues, and I will wait for results of long-term effects on neonatal outcomes, studies using biomarkers for risk assessment of women at risk for adverse outcomes, and opinions from ACOG and the Society for Maternal-Fetal Medicine about this management plan.

SAROSH RANA, MD, MPH

The takeaway

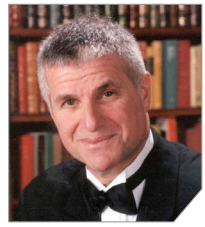
In the absence of biomarkers for risk stratification and treatment of preeclampsia, delivering women who have a diagnosis of preeclampsia at or beyond 34 weeks' gestation may be a viable option for preventing maternal complications. ●

Reference

1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Gestational hypertension and preeclampsia. *Obstet Gynecol.* 2019;133:e1-e25.

Coming soon...

- **Managing eating disorders in pregnancy**
  Gianna Wilkie, MD; Leena Mittal, MD; and Nicole Smith, MD, MPH
- **Update on obstetrics**
  Jaimey Pauli, MD
- **Break the Practice Habit: It's time to stop using opioids after vaginal delivery, and to decrease use after cesarean**
  Erica Holland, MD, and Julian N. Robinson, MD



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In this Update: BMD testing—understanding who to scan and what sites to evaluate, ospemifene's effects on bone, assessing for sarcopenia as well as osteoporosis, and aromatase inhibitors and treatment for fracture prevention

Prior to last year, this column was titled "Update on osteoporosis." My observation, however, is that too many ObGyn providers simply measure bone mass (known as bone mineral density, or BMD), label a patient as normal, osteopenic, or osteoporotic, and then consider pharmacotherapy. The FRAX fracture prediction algorithm, which incorporates age, weight, height, history of any previous fracture, family history of hip fracture, current smoking, use of glucocorticoid medications, and any history of rheumatoid arthritis, has refined the screening process somewhat, if and when it is utilized. As clinicians, we should never lose sight of our goal: to prevent fragility fractures. Having osteoporosis increases that risk, but not having osteoporosis does not eliminate it.

In this Update, I highlight various ways in which work published this past year may help us to improve our patients' bone health and reduce fragility fractures.

IN THIS ARTICLE

Updated ISCD guidance emphasizes appropriate BMD testing, use of the Z-score, and terminology

International Society for Clinical Densitometry. 2019 ISCD Official Positions–Adult. June 2019. https://www.iscd.org/official-positions/2019-ISCD-official-positions-adult.

In 2019, the International Society for Clinical Densitometry (ISCD) updated all its official positions from 2015.[1] I will summarize the points that are important for ObGyn providers. We are and should be, I believe, the first-line protectors of women's bone health.

Indications for BMD testing

The ISCD's indications for BMD testing remain for women age 65 and older. For postmenopausal women younger than age 65, a BMD test is indicated if they have a risk factor for low bone mass, such as 1) low body weight, 2) prior fracture, 3) high-risk medication use, or 4) a disease or condition associated with bone loss. A BMD test also is indicated for women during the menopausal transition with clinical risk factors for fracture, such as

low body weight, prior fracture, or high-risk medication use. Interestingly, the ISCD recommendation for men is similar but uses age 70 for this group.

In addition, the ISCD recommends BMD testing in adults with a fragility fracture, with a disease or condition associated with low bone mass, or taking medications associated with low bone mass, as well as for anyone being considered for pharmacologic therapy, being treated (to monitor treatment effect), not receiving therapy in whom evidence of bone loss would lead to treatment, and in women discontinuing estrogen who should be considered for BMD testing according to the indications already mentioned.

Sites to assess for osteoporosis. The World Health Organization international reference standard for osteoporosis diagnosis is a T-score of -2.5 or less at the femoral neck. The reference standard, from which the T-score is calculated, is for white women aged 20 to 29 years of age from the database of the Third National Health and Nutrition Examination Survey. Osteoporosis also may be diagnosed in postmenopausal women if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less. In certain circumstances, the 33% radius (also called the one-third radius) may be utilized. Other hip regions of interest, including Ward's area and the greater trochanter, should *not* be used for diagnosis.

The skeletal sites at which to measure BMD include the anteroposterior of the spine and hip in all patients. In terms of the spine, use L1–L4 for spine BMD measurement. However, exclude vertebrae that are affected by local structural changes or artifact. Use 3 vertebrae if 4 cannot be used, and 2 if 3 cannot be used. BMD-based diagnostic classification should not be made using a single vertebra. Anatomically abnormal vertebrae may be excluded from analysis if they are clearly abnormal and nonassessable within the resolution of the system, or if there is more than a 1.0 T-score difference between the vertebra in question and adjacent vertebrae. When vertebrae are excluded, the BMD of the remaining vertebrae are used to derive the T-score.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Patients commonly ask for BMD testing and ObGyn providers commonly order it. Understanding appropriate use of BMD testing in terms of who to scan, what sites to evaluate, when there may be spurious results of vertebrae due to artifacts, avoiding T-scores in premenopausal women in favor of Z-scores, understanding that *low bone mass* is a preferred term to *osteopenia,* and knowing how to order and use serial BMD testing will likely improve our role as the frontline providers to improving bone health in our patients.

For BMD measurement at the hip, the femoral neck or total proximal femur—whichever is lowest—should be used. Either hip may be measured. Data are insufficient on whether mean T-scores for bilateral hip BMD should be used for diagnosis.

Terminology. While the ISCD retains the term *osteopenia*, the term *low bone mass* or *low bone density* is preferred. People with low bone mass or density are not necessarily at high fracture risk.

Concerning BMD reporting in women prior to menopause, Z-scores, not T-scores, are preferred. A Z-score of -2.0 or lower is defined as "below the expected range for age"; a Z-score above -2.0 is "within the expected range for age."

Use of serial BMD testing

Finally, regarding serial BMD measurements, such testing in combination with clinical assessment of fracture risk can be used to determine whether treatment should be initiated in untreated patients. Furthermore, serial BMD testing can monitor a patient's response to therapy by finding an increase or stability of bone density. It should be used to monitor individuals following cessation of osteoporosis drug therapy. Serial BMD testing can detect loss of bone density, indicating the need to assess treatment adherence, evaluate possible secondary causes of osteoporosis, and possibly re-evaluate therapeutic options.

Intervals between BMD testing should be determined according to each patient's clinical status. Typically, 1 year after initiating or changing therapy is appropriate, with longer intervals once therapeutic effect is established.

FAST TRACK

The ISCD recommends BMD testing in adults with a fragility fracture, with a condition associated with low bone mass, or taking medications associated with low bone mass

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Dyspareunia drug has positive effects on bone

de Villiers TJ, Altomare C, Particco M, et al. Effects of ospemifene on bone in postmenopausal women. Climacteric. 2019;22:442-447.

Ospemifene is a selective estrogen receptor modulator (SERM), given daily and orally, that was approved by the US Food and Drug Administration (FDA) in 2013 for moderate to severe dyspareunia due to menopause-related vulvovaginal atrophy (VVA). More recently, the indication has been extended to include vaginal dryness of menopause. Other SERMs have shown efficacy in prevention and treatment of osteoporosis, including raloxifene, which was FDA approved for the respective indications in 1997 and 1999, and lasofoxifene, which showed efficacy but was not approved in the United States.[2]

Previously, ospemifene effectively reduced bone loss in ovariectomized rats, with activity comparable to that of estradiol and raloxifene.[3] Clinical data from 3 phase 1 or 2 clinical trials found that ospemifene 60 mg/day had a positive effect on biochemical markers for bone turnover in healthy postmenopausal women, with significant improvements relative to placebo and effects comparable to those of raloxifene.[4]

Effects on bone formation/resorption biomarkers

In a recent study, de Villiers and colleagues reported the first phase 3 trial that looked at markers of bone formation and bone resorption.[5] A total of 316 women were randomly assigned to receive ospemifene, and 315 received placebo.

Demographic and baseline characteristics were similar between treatment groups. Participants' mean age was approximately 60 years, mean body mass index (BMI) was 27.2 kg/m^2, and mean duration of VVA was 8 to 9 years. Serum levels of 9 bone biomarkers were similar between groups at baseline.

At week 12, all 5 markers of bone resorption improved with ospemifene treatment, and 3 of the 5 (NTX, CTX, and TRACP-5b) did so in a statistically significant fashion compared with placebo ($P \leq .02$). In addition, at week 12, all 4 markers of bone formation improved with ospemifene treatment compared with placebo ($P \leq .008$). Furthermore, lower bone resorption markers with ospemifene were observed regardless of time since menopause (≤ 5 years or > 5 years) or baseline BMD, whether normal, osteopenic, or osteoporotic.

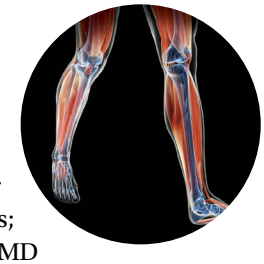
Interpret results cautiously

The authors caution that the data are limited to biochemical markers rather than fracture or BMD. It is known that there is good correlation between biochemical markers for bone turnover and the occurrence of fracture.[6]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Ospemifene is an oral SERM approved for the treatment of moderate to severe dyspareunia as well as dryness from VVA due to menopause. The preclinical animal data and human markers of bone turnover all support the antiresorptive action of ospemifene on bones. Thus, one may safely surmise that ospemifene's direction of activity in bone is virtually indisputable. The magnitude of that activity is, however, unstudied. Therefore, when choosing an agent to treat women with dyspareunia or vaginal dryness from VVA of menopause, determining any potential add-on benefit in bone may be appropriate for that particular patient, although one would not use it as a stand-alone agent for bone only.

Sarcopenia adds to osteoporotic risk for fractures



Lima RM, de Oliveira RJ, Raposo R, et al. Stages of sarcopenia, bone mineral density, and the prevalence of osteoporosis in older women. Arch Osteoporos. 2019;14:38.

Osteoporotic fractures impose a significant burden on health care costs and increase the risk for disability and mortality, especially as life expectancy increases.[7]

In 1989, the term *sarcopenia* was introduced to refer to the age-related decline in skeletal muscle mass.[8] Currently, sarcopenia is defined as a progressive decline in muscle mass, strength, and physical function, thus increasing the risk for various adverse outcomes, including osteoporosis.[9] Although muscle and bone tissues differ morphologically, their functioning is closely interconnected.

The sarcopenia-osteoporosis connection

Lima and colleagues sought to investigate the relationship between sarcopenia and osteoporosis.[10] They measured women's fat free mass with dual-energy x-ray absorptiometry (DXA) scanning, muscle strength using a dynamometer to measure knee extension torque while participants were seated, and functional performance using the timed "up and go test" in which participants were timed as they got up from a chair, walked 3 meters around a cone, and returned to sit in the chair.[10,11]

The authors used definitions from the European Working Group on Sarcopenia in Older People (EWGSOP). Participants who had normal results in all 3 domains were considered nonsarcopenic. Presarcopenia was defined as having low fat free mass on DXA scanning but normal strength and function. Participants who had low fat free mass and either low strength or low function were labeled as having sarcopenia. Severe sarcopenia was defined as abnormal results in all 3 domains.

Two hundred thirty-four women (mean age, 68.3 years; range, 60–80) underwent BMD testing and were evaluated according to the 3 domains of possible sarcopenia. All were community dwelling and did not have cognitive impairment or functional dependency.

The rates of osteoporosis were 15.8%, 19.2%, 35.3%, and 46.2% for nonsarcopenia, presarcopenia, sarcopenia, and severe sarcopenia, respectively ($P=.002$). Whole-body and femoral neck BMD values were significantly lower among all sarcopenia stages when compared with nonsarcopenia ($P<.05$). The severe sarcopenia group showed the lowest lumbar spine T-scores ($P<.05$). When clustered, sarcopenia and severe sarcopenia presented a significantly higher risk for osteoporosis (odds ratio, 3.4; 95% confidence interval [CI], 1.5–7.8).

Consider sarcopenia a risk factor

The authors concluded that these "results provide support for the concept that a dose-response relationship exists between sarcopenia stages, BMD, and the presence of osteoporosis. These findings strengthen the clinical significance of the EWGSOP sarcopenia definitions and indicate that severe sarcopenia should be viewed with attention by healthcare professionals."

FAST TRACK

When clustered, sarcopenia and severe sarcopenia presented a significantly higher risk for osteoporosis (OR, 3.4; 95% CI, 1.5–7.8)

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Osteoporotic fractures are defined as fragility fractures. While "frailty" has been a risk factor for such fractures in the past, increasing evidence now suggests that what we previously called frailty includes a significant component of loss of muscle mass, strength, and function—referred to as sarcopenia. While it is not likely that many ObGyns will perform objective testing for sarcopenia, conducting even a subjective assessment of such status should be considered in addition to BMD determinations in making decisions about pharmacotherapy.

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Certain characteristics may offset fracture risk in aromatase inhibitor users

Leslie WD, Morin SN, Lix LM, et al. Fracture risk in women with breast cancer initiating aromatase inhibitor therapy: a registry-based cohort study. Oncologist. 2019;24:1432-1438.

FAST TRACK

After adjusting for all covariates, AI users were not at significantly greater risk for major osteoporotic fractures, hip fracture, or any fracture compared with the general population

As ObGyn providers, we often treat women who have been diagnosed and treated for breast cancer. Initially, tamoxifen was the mainstay of hormonal adjuvant therapy. More recently, aromatase inhibitors (AIs) have played an increasing role in the treatment of women with estrogen receptor–positive breast cancer.[12]

The use of AIs increases bone turnover and induces bone loss at trabecular-rich bone sites at an average rate of 1% to 3% per year, with reports of up to a threefold increased fracture incidence.[13] By contrast, a large nationwide population-based cohort study using US Medicare data identified minimal fracture risk from AI use compared with tamoxifen use (11% higher for nonvertebral fractures, not significantly increased for hip fractures).[14]

An article published previously in this column reported that women on AIs treated with intravenous zoledronic acid had improvements in BMD, while women treated with denosumab had statistically significant fewer fractures compared with those receiving placebo, whether they had normal bone mass, osteopenia, or osteoporosis at baseline.[15-17]

Data derived from a population-based BMD registry

In a recent cohort study, Leslie and colleagues offer the opinion that "observations in the clinical trial setting may differ from routine clinical practice."[18] The authors examined fracture outcomes using a large clinical registry of BMD results from women in Manitoba, Canada. They identified women at least 40 years of age initiating AI therapy for breast cancer (n = 1,775), women with breast cancer not receiving AI therapy (n = 1,016), and women from the general population without breast cancer (n = 34,205).

Fracture outcomes were assessed after a mean of 6.2 years for the AI users, all of whom had at least 12 months of AI exposure. At baseline, AI users had higher BMI, higher BMD, lower osteoporosis prevalence, and fewer prior fractures than women from the general population or women with breast cancer without AI use (all $P<.001$). After adjusting for all covariates, AI users were not at significantly greater risk for major osteoporotic fractures (hazard ratio [HR], 1.15; 95% CI, 0.93–1.42), hip fracture (HR, 0.90; 95% CI, 0.56–1.43), or any fracture (HR, 1.06; 95% CI, 0.88–1.28) compared with the general population.

Results challenge prevailing view

Thus, the authors concluded that higher baseline BMI, BMD, and lower prevalence of prior fracture at baseline may offset the adverse effects of AI exposure. Although confirmatory data from large cohort studies are required, the authors stated that their findings challenge the view that all women with breast cancer initiating AI therapy should be considered at high risk for fracture. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

It is well known that women with estrogen receptor–positive breast cancers tend to be more obese than noncancer patients and have higher levels of circulating estrogens. The study by Leslie and colleagues shows that such patients will have fewer previous fractures and better baseline bone mass values than the general population. This may prompt us to rethink whether *all* women initiating AI therapy need to be treated for fracture prevention, as some previous studies have suggested. Clearly, further study is necessary.

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COMMENTARY

The One Step test: The better diagnostic approach for gestational diabetes mellitus

It is time for the United States to reconsider its guidelines for screening for GDM

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Gestational diabetes mellitus (GDM) generally is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1-14] The best approach and exact criteria to use for GDM screening and diagnosis are under worldwide debate. In **TABLE 1** we present just some of the many differing suggestions by varying organizations.[2,7-9,11,12,15-17] The American College of Obstetricians and Gynecologists, for instance, suggests a Two Step approach to diagnosis.[15] We will make the argument in this article, however, that diagnosis should be defined universally as an abnormal result with the One Step 75-g glucose testing, as adopted by the World Health Organization, International Federation of Gynecology and Obstetrics, and others. Approximately 8% of all pregnancies are complicated by GDM by the One Step test in the United States.[18-22] The prevalence may range from 1% to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed.[1,19]

The authors report no financial relationships relevant to this article.

Diagnostic options

Different methods for screening and diagnosis of GDM have been proposed by international societies; there is controversy regarding the diagnosis of GDM by either the One Step or the Two Step approach.[6]

The One Step approach includes an oral glucose tolerance test with a 75-g glucose load with measurement of plasma glucose concentration at fasting state and 1 hour and 2 hours post–glucose administration. A positive result for the One Step approach is defined as at least 1 measurement higher than 92, 180, or 153 mg/dL at fasting, 1 hour, or 2 hours, respectively.

The Two Step approach includes a nonfasting oral 50-g glucose load, with a glucose blood measurement 1 hour later. A positive screening, defined often as a blood glucose value higher than 135 mg/dL (range, 130 to 140 mg/dL), is followed by a diagnostic test with a 100-g glucose load with measurements at fasting and 1, 2, and 3 hours post–glucose administration. A positive diagnostic test is defined as 2 measurements higher than the target value.

Why we support the One Step test

There are several reasons to prefer the One Step approach for the diagnosis of GDM, compared with the Two Step approach.

Women testing negative for GDM with Two Step still experience complications pregnancy. Women who test positive for GDM with the One Step test, but negative with the Two Step test, despite having therefore a milder degree of glucose intolerance, do have a higher risk of experiencing several complications.[23] For the mother, these complications include gestational hypertension, preeclampsia, and cesarean delivery. The baby also can experience problems at birth (**TABLE 2**).[23] Therefore, women who test positive for GDM with the One Step test deserve to be diagnosed with and treated for the condition, as not only are they at risk for these complications but also treatment of the GDM decreases the incidence of these complications.[18,19]

There is indeed an increased GDM diagnosis rate with the One Step (about 8%) compared with

TABLE 1 Criteria for gestational diabetes mellitus screening by selected societies[2,7-9,11,12,15-17]

Society	Test	No. of abnormal values required for diagnosis	Fasting glucose (mg/dL)	1 hour after loading (mg/dL)	2 hours after loading (mg/dL)	3 hours after loading (mg/dL)
ACOG 2017[15]; C&C[16]	Two Step 3-hr 100 g	≥2	95	180	155	140
ACOG 2017[15]; NDDG[17]	Two Step 3-hr 100 g	≥2	105	190	165	145
ADA 2017[7] 75 g	One Step 2-hr 75 g	≥2	95	180	155	Not required
ADA 2017[7] 100 g	Two Step 3-hr 100 g	≥2	95	180	155	140
CDA 2013[8]	Two Step 2-hr 75 g	≥2	95	191	160	Not required
FIGO 2013[12]	One Step 2-hr 75 g	≥1	92	180	153	Not required
IADPSG 2015[2,12]	One Step 2-hr 75 g	≥1	92	180	153	Not required
NICE/RCOG 2015[9]	One Step 2-hr 75 g	≥1	101	Not required	140	Not required
WHO 2013[11]	One Step 2-hr 75 g	≥1	92	180	153	Not required

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; C&C, Carpenter and Coustan; FIGO, International Federation of Gynecology and Obstetrics; IADPSG, International Association of Diabetes Pregnancy Study Group; NICE, National Institute for Health and Care Excellence; RCOG, Royal College of Obstetricians and Gynecologists; NDDG, National Diabetes Data Group; WHO, World Health Organization.

the Two Step test (about 4%). Nonetheless, this increase is mild and nonsignificant in the meta-analysis of randomized controlled trials (RCTs),[18,19] is less than the 18% difference in diagnosis rate previously hypothesized, is consistent with the increased diabetes/prediabetes rates in the general population, and is linked to the increasing incidence of obesity and insulin resistance.

Overall test adherence is better. Five percent to 15% of patients, depending on the study, are not adherent with taking the second part of the Two Step test. Women indeed prefer the One Step approach; the second step in the Two Step approach may be a burden.

Less costly. The One Step process is cost-effective when postpregnancy diabetes mellitus prevention is considered.

Better maternal and perinatal outcomes. Probably the most important and convincing reason the One Step test should be used is that meta-analysis of the 4 RCTs comparing the approaches (including 2 US trials) shows that diagnosing and treating mild GDM as per the One Step approach, compared with screening and treating using the Two Step approach, is associated with increased incidence of GDM (8% vs 4%) and with better maternal and perinatal outcomes.[13,18,19] In fact, the One Step approach is associated with significant reductions in: large for gestational age (56%), admission to neonatal intensive care unit (51%), and neonatal hypoglycemia (48%). Tests of heterogeneity in the meta-analysis and of quality all pointed to better outcomes in the One Step test group.[13,19]

The need for a second step in the Two Step approach delays diagnosis and treatment. The One

TABLE 2 Complication risks in pregnancies that are positive for GDM at the One Step test but negative at the Two Step test compared with pregnancies that are negative at the One Step test[23]

Maternal	Neonatal
Gestational hypertension	Preterm birth
Preeclampsia	Macrosomia/LGA
Cesarean delivery	Hypoglycemia
	Intensive care unit admission

Abbreviations: GDM, gestational diabetes mellitus; LGA, large for gestational age.

TABLE 3 Benefits of the One Step approach, compared with the Two Step approach

- The increased GDM rate (8% with One Step vs 4% with Two Step) is consistent with the increased diabetes/prediabetes rates in the general population
- Better adherence, as patients may not be adherent with the second part of the Two Step test
- Milder GDM (positive One Step test, but negative Two Step) is associated with several maternal and perinatal adverse outcomes, compared with euglycemic women (see TABLE 2)[23]
- The One Step process is cost-effective when postpregnancy DM prevention is considered
- Meta-analysis of RCTs[19] shows that diagnosing and treating mild GDM as per the One Step approach, compared with screening and treating using the Two Step approach, is associated with several benefits, including less:
  - Preeclampsia[a]
  - Large for gestational age
  - Neonatal hypoglycemia
  - NICU admission
  - Neonatal death[a]
- The need for a second step in the Two Step approach delays diagnosis and treatment of GDM
- The One Step, 75-g, 2-hour OGTT is universally used outside of pregnancy

Abbreviations: GDM, gestational diabetes mellitus; DM, diabetes mellitus; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test; RCT, randomized controlled trial.

[a]Statistical trends.

Step approach is associated with an increase in GDM test adherence and earlier diagnosis,[13] which is another reason for better outcomes with the One Step approach. In the presence of risk factors, such as prior GDM, prior macrosomia, advanced maternal age, multiple gestations, and others, the One Step test should be done at the first prenatal visit.

US guidelines should be reconsidered

The One Step, 75-g, 2-hour oral glucose tolerance test is universally used to diagnose diabetes mellitus outside of pregnancy. Given our many noted reasons (**TABLE 3**), we recommend universal screening of GDM by using the One Step approach. It is time, indeed, for the United States to reconsider its guidelines for screening for GDM. ●

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OBG MANAGEMENT

Preventing early-onset group B streptococcal disease in newborns

7 patient questions about GBS answered

Patrick Duff, MD

IN THIS ARTICLE

In 1992, the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) published their first joint guidelines on the prevention of early-onset neonatal group B streptococcal (GBS) infection.[1] In this initial statement, the organizations recommended universal culturing of obstetric patients at 28 weeks' gestation and treatment of colonized women during labor if they had a recognized risk factor for neonatal GBS infection.

In 1996, the Centers for Disease Control and Prevention (CDC) published its first set of official guidelines on the topic and suggested that both universal screening and a risk-factor–based approach were reasonable options.[2] The 2002 update of the CDC guidelines strongly recommended universal screening of all pregnant women at 35 to 37 weeks' gestation and intrapartum prophylaxis for all colonized women regardless of risk factors.[3]

The third set of CDC guidelines was published in 2010.[4] The key features of this version were the elimination of erythromycin as an alternative to penicillin in patients who are allergic to beta-lactam antibiotics and the establishment of 4 hours as the critical interval for administration of prophylaxis prior to delivery. The 2010 publication was the last such report from the CDC. Since then ACOG and AAP have been tasked with providing updated practice guidelines. To that end, ACOG recently issued a new Committee Opinion on "Prevention of Group B Streptococcal Early-Onset Disease in Newborns."[5] Here we will highlight the key features of our current strategy for preventing neonatal GBS infection.

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CASE Pregnant patient presents with many questions about GBS

A 26-year-old primigravid woman presents for her first prenatal appointment at 9 weeks' gestation. Her older sister recently delivered a term infant that died in the first week of life from GBS sepsis. Understandably, she has many questions.

1 Your patient first wants to know, "What is this streptococcal organism and how likely am I to have this infection?"

Streptococcus agalactiae, also known as GBS, is a gram-positive encapsulated bacterium that produces beta hemolysis when grown on blood agar. Approximately 25% of pregnant women harbor this organism in the lower genital tract and/or rectum.[6]

GBS is one of the most important causes

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of neonatal infection, particularly in preterm infants. The frequency of infection is now 0.23 per 1,000 live births in the US.[5]

Neonatal infection can be divided into early-onset infection (occurring within the first 7 days of life) and late-onset infection (occurring from after the first week until the third month of life). Approximately 80% to 85% of cases of neonatal GBS infections are early in onset. Virtually all of the early-onset infections result from vertical transmission during delivery from a colonized mother to her infant.[5-7]

2 "How dangerous is this infection to my baby and me? Are there certain factors that increase the risk of my baby becoming infected?"

GBS is responsible for approximately 2% to 3% of cases of either asymptomatic bacteriuria or acute cystitis. Women with urinary tract infections caused by GBS are at increased risk for preterm premature rupture of membranes and preterm delivery. Genital tract colonization also increases a woman's risk for chorioamnionitis and endometritis, particularly after cesarean delivery (CD). In addition, GBS can be part of the polymicrobial flora in women who have a wound (incisional site) infection following CD.[6,7]

In colonized women, several risk factors have been identified that increase the probability of early-onset neonatal GBS infection. These factors include: preterm labor, especially when complicated by premature rupture of membranes; intrapartum maternal fever (usually due to chorioamnionitis); rupture of membranes greater than 18 hours before delivery; previous delivery of an infected infant; young age; and black or Hispanic ethnicity. Approximately 25% of colonized women will have one of these risk factors.[5-7]

These risk factors have a profound impact on neonatal attack rates and mortality. Without the interventions outlined below, the neonatal infection rate is 40% to 50% in the presence of a risk factor and less than 5% in the absence of a risk factor. In infected infants, neonatal mortality approaches 30% to 35% when a maternal risk factor is present, but is less than 5% when risk factors are absent.[5-7]

3 "What will you do to determine if I am colonized with this organism?"

The current guidelines set forth in the ACOG Committee Opinion recommend that selected high-risk patients (patients with preterm labor or preterm premature rupture of membranes) be tested for GBS at the time of initial presentation. All other women should be tested for GBS during the interval 36 0/7 to 37 6/7 weeks' gestation.[5] Testing at this point in pregnancy is almost 90% sensitive for identifying patients who will be colonized at the time of admission for labor if no more than 5 weeks elapse between the time the culture is obtained and labor begins. The positive predictive value of this test is 87%, and the negative predictive value is 96%.[8]

ACOG's previous guidelines provided for testing at 35 rather than 36 weeks. The change in the recommendations was based on 2 factors. First, all women with unknown GBS status who may deliver before 37 weeks already should be targeted for prophylaxis. Second, the new 5-week window now will include women who deliver up to 41 weeks' gestation. Given current obstetric practice in the US, delivery beyond 41 weeks is unlikely.[5]

At the present time, the best test for identification of GBS colonization is bacteriologic culture. A cotton swab is placed into the lower third of the vagina, streaked along the perineum, and then placed into the rectum. The swab is withdrawn, placed in a culturette tube, and transported to the laboratory. In the laboratory, the swab is cultured for approximately 24 hours in a nutrient broth and then subcultured on a selective blood agar plate. Failure to sample both the vagina and rectum or failure to use selective broth and selective blood agar will reduce the yield of positive cultures by approximately 50%.[5-7]

In recent years, researchers have become interested in the use of rapid nucleic acid amplification tests for the identification of GBS. These tests perform well if the

FAST TRACK

All women should be tested for GBS during the interval 36 0/7 to 37 6/7 weeks' gestation. Patients with preterm labor or preterm premature rupture of membranes should be tested at initial presentation.

test protocol provides for an 18- to 24-hour incubation in nutrient broth prior to application of the nucleic acid probe. When the tests are performed without this enrichment phase, sensitivities are inferior to those associated with bacteriologic culture. In addition, because the rapid tests do not isolate the organisms, they do not allow for antibiotic sensitivity testing.[5-7]

4 "If I test positive for GBS, how and when will you treat me?"

The current ACOG guidelines recommend that all colonized women be treated intrapartum with prophylactic antibiotics regardless of whether risk factors are present. Treatment should be started at the time of admission and continued until the infant is delivered.[5]

The drugs of choice for intrapartum prophylaxis are intravenous penicillin or ampicillin. If the patient has a mild allergy to penicillin, cefazolin is the appropriate alternative. If the patient has a severe allergy to penicillin, the 2 options are vancomycin or clindamycin. If the latter drug is used, the laboratory must perform sensitivity testing because 13% to 20% of strains of GBS may be resistant to clindamycin. The frequency of resistance to erythromycin now ranges from 25% to 32%. Thus, erythromycin is no longer used for intrapartum prophylaxis.[5-7,9]

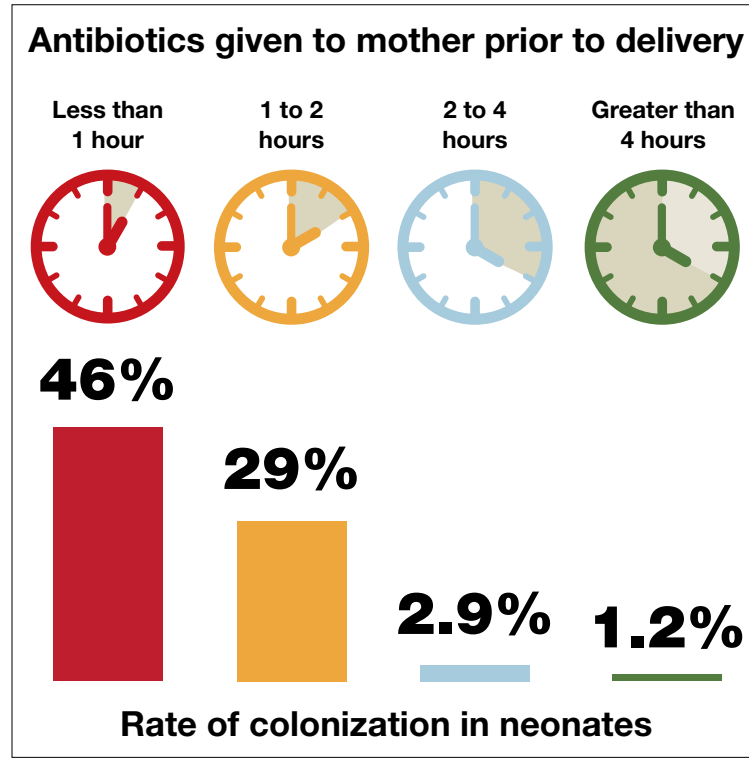
The appropriate intravenous dosages of these antibiotics are listed in the **TABLE**.[5] The new ACOG guidelines have revised the previous recommendations for dosing of penicillin, eliminating the 2.5 million-unit dose. They also have revised the dosing recommendations for vancomyin, eliminating the previous recommendation of 1 g every 12 hours.[5] The new recommendations regarding vancomycin are particularly important and are based, at least in part, on an interesting report from Onwuchuruba and colleagues.[10] These authors studied maternal and cord blood concentrations of vancomycin in mother-infant dyads receiving either the original recommended dosage of vancomycin (1 g every 12 hours) or a dosage of 15 to 20 mg/kg every 8 hours. With standard dosing, only 9% of neonates had therapeutic vancomycin serum concentrations at delivery. With the 20 mg/kg dose of vancomycin, the percent of neonates with therapeutic serum concentrations of vancomycin increased to 80%.

TABLE Intravenous antibiotic dosing regimens for GBS prophylaxis[5]

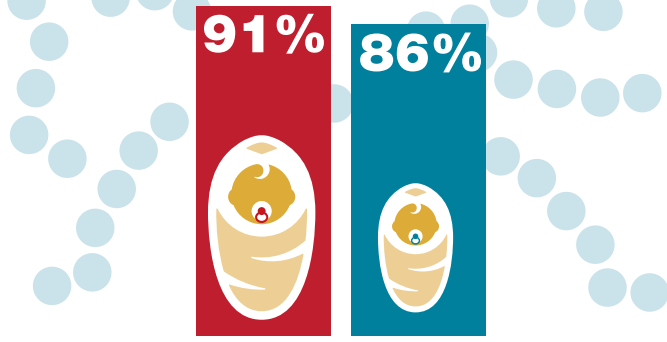
Drug	Dose
Ampicillin	2 g initially, then 1 g every 4 hours
Cefazolin	2 g initially, then 1 g every 8 hours
Clindamycin	900 mg every 8 hours
Penicillin	5 million units initially, then 3 million units every 4 hours
Vancomycin	20 mg/kg every 8 hours Maximum of 2 g per single dose Dose should be infused over 1 to 2 hours

5 "For how long must I be treated in labor before my baby will be protected by the antibiotics?"

The current ACOG Committee Opinion stresses the importance of treating the colonized mother for at least 4 hours prior to delivery.[5] This recommendation is based primarily on the landmark report by De Cueto



Prophylaxis with penicillin or ampicillin for 4 hours or more was **91%** effective in preventing early-onset neonatal infection in term infants and **86%** effective in preventing infection in preterm infants.



FAST TRACK

Women undergoing scheduled CD should have a GBS culture between 36 0/7 to 37 6/7 weeks' gestation, but if they do not experience spontaneous delivery they do not require GBS prophylaxis at surgery

and colleagues.[11] These authors evaluated colonized women who received intrapartum prophylaxis at varying times prior to delivery. Their primary endpoint was the percentage of newborns who were colonized with GBS. If the mothers had received antibiotics for less than 1 hour prior to delivery, 46% of neonates were colonized. This figure was equal to the rate of colonization in neonates whose mothers received no antibiotics. When the interval was 1 to 2 hours, the percentage was 29%. When mothers had received antibiotics for 2 to 4 hours, the neonatal colonization rate fell to 2.9%. When antibiotics had been administered for greater than 4 hours, the rate of neonatal colonization was only 1.2%.

Fairlie and colleagues recently reported the results of another interesting investigation comparing the effectiveness of prophylaxis based on duration of treatment and choice of individual antibiotics.[12] Prophylaxis with penicillin or ampicillin for 4 hours or more was 91% effective in preventing early-onset neonatal infection in term infants and 86% effective in preventing infection in preterm infants. These outcomes were superior to the outcomes in both term and preterm infants who received penicillin or ampicillin for less than 4 hours.

These observations agree with the findings of McNanley and colleagues who evaluated vaginal colony counts of GBS following different periods of antibiotic administration.[13] These authors noted that mean colony counts decreased 5-fold within 2 hours of penicillin administration, 50-fold within 4 hours, and 1,000-fold within 6 hours.

Despite these compelling findings, the ACOG Committee Opinion stresses that obstetric interventions such as amniotomy and oxytocin augmentation should not be delayed simply to permit a certain time period of antibiotic administration.[5]

6 "If I were to have a scheduled CD before the onset of labor and/or ruptured membranes, would I still need to receive antibiotics?"

If a mother is scheduled to have a CD, for example because of a prior cesarean or because of a persistent fetal malpresentation, she should still have a GBS culture at 36 0/7 to 37 6/7 weeks' gestation. The information obtained from this culture may be of value to both the obstetrician and pediatrician if the patient experiences labor or rupture of membranes prior to her scheduled surgery. If she does not experience spontaneous labor prior to her scheduled date of surgery, she does not require specific GBS prophylaxis at the time of her operation.[5] Rather, she should receive prophylactic antibiotics to prevent post–cesarean infection, ideally, the combination of cefazolin (2 g IV) plus azithromycin (500 mg IV).[14] Cefazolin, of course, provides excellent coverage of GBS.

7 "If I am colonized with GBS and I receive treatment during labor, will my baby be safe after delivery?"

The interventions outlined above will prevent almost 90% of early-onset GBS infections, but they are not foolproof.[5-7,15,16] Successful management of the neonate is dependent upon several factors, including:[5-7]

- gestational age
- presence of maternal chorioamnionitis
- presence or absence of risk factors for early-onset infection
- duration (adequacy) of maternal treatment

during labor

- presence of immediate clinical signs of infection in the neonate (such as fever, lethargy, hemodynamic instability, respiratory distress, or elevated or decreased white blood cell count).

If the mother is at term and receives intrapartum prophylaxis for at least 4 hours prior to delivery, the neonate usually will not require any special tests and simply will be observed for 24 to 48 hours for signs of infection.

If the mother delivers preterm and receives appropriate intrapartum prophylaxis, the pediatricians typically will obtain a complete blood count (CBC) and treat with prophylactic antibiotics (ampicillin plus gentamicin) for 48 hours if abnormalities are noted on the CBC or the baby exhibits signs of infection. If the CBC is normal and the baby shows no signs of infection, no treatment is indicated.

Regardless of gestational age, if the mother does not receive prophylaxis for at least 4 hours before delivery, the pediatricians usually will obtain a CBC and closely observe the baby in the hospital for signs of infection. If such signs develop or the CBC is abnormal, blood and cerebrospinal fluid cultures will be obtained. Antibiotic therapy (usually ampicillin plus gentamicin) is then initiated, and the drugs are continued until cultures return with no growth. If either culture is positive, antibiotics will then be continued for 7 to 10 days.

If the mother has documented chorioamnionitis and receives treatment intrapartum with appropriate antibiotics (usually ampicillin plus gentamicin), the pediatricians usually will obtain a CBC, C-reactive protein (CRP) level, and blood cultures and then start the infant on antibiotics, pending the result of the laboratory tests. If the CBC and CRP are reassuring, the cultures are negative after 48 hours, and the infant demonstrates no signs of clinical infection, many pediatricians will then discontinue antibiotics. Others may still continue the antibiotics for 7 to 10 days. ●

FAST TRACK

Regardless of gestational age, if a GBS-positive mother does not receive prophylaxis for at least 4 hours before delivery, the baby will have a CBC and be closely observed for signs of infection

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Persistent vulvar itch

A case of pink, symmetrical bilateral plaques on the labia majora, without evidence of atrophy or scarring and with scant white vaginal discharge

Kerrie G. Satcher, MD; Stephanie J. Carstens, MD; and Andrew M. Kaunitz, MD, NCMP

FIGURE 1 Bilateral labia majora show lichenification

On bilateral labia majora, symmetric, pink plaques with accentuated skin markings (lichenification) noted on physical examination. Scant white vaginal discharge was noted on exam but is inconspicuous in photo.

CASE Lingering vulvar pruritus developed during traveling

A 48-year-old premenopausal Hispanic woman with past medical history of breast cancer presents to a dermatologist with the chief complaint of persistent vulvar pruritus. The vulvar itching began while traveling and has continued for 6 months. Previous treatments have been trialed, including over-the-counter feminine hygiene products, wipes, and hydrocortisone ointment.

Physical examination reveals pink, symmetric, bilateral lichenified plaques on the labia majora, without evidence of atrophy or scarring (**FIGURE 1**). Scant white vaginal discharge is also noted.

What is the most likely diagnosis?

- Genital lichen simplex chronicus
- Genital atopic dermatitis
- Genital lichen sclerosus

Turn the page to see if you are correct.

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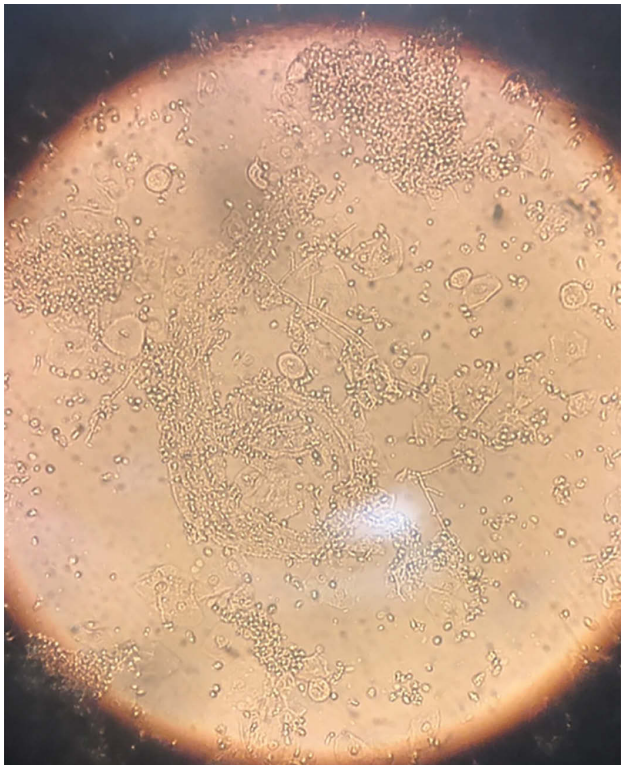
Genital lichen simplex chronicus

Lichen simplex chronicus (LSC) is an inflammatory skin condition that develops secondary to persistent rubbing or scratching of skin. Although LSC can occur anywhere on the body, genital LSC develops in association with genital itch, with the itch often described as intense and unrelenting. The itching sensation leads to scratching and rubbing of the area, which can provide temporary symptomatic relief.[1,2] However, this action of rubbing and scratching stimulates local cutaneous nerves, inducing an even more intense itch sensation. This process, identified as the 'itch-scratch cycle,' plays a prominent role in all cases of LSC.[1]

On physical examination LSC appears as poorly defined, pink to red plaques with accentuated skin markings on bilateral labia majora. Less commonly, it can present as asymmetrical or unilateral plaques.[3] LSC can extend onto labia minora, mons pubis, and medial thighs. However, the vagina is spared.[1] Excoriations, marked by their geometric, angular appearance, often can be appreciated overlying plaques of LSC. Additionally, crusting, scale, broken hairs, hyperpigmentation, and scarring may be seen in LSC.[2]

FIGURE 2 Wet mount of vaginal discharge, revealing candida hyphae and spores



In this case, white discharge was noted on vaginal examination, which was suspicious for vaginal candidiasis. Wet mount examination revealed multiple candida hyphae and spores (**FIGURE 2**), confirming vaginal candidiasis. This vulvovaginal fungal infection caused persistent vulvar pruritus, with subsequent development of LSC due to prolonged scratching. The patient was treated with both oral fluconazole and topical mometasone ointment, for vaginal candidiasis and vulvar LSC, respectively. Mometasone ointment is categorized as a class II (high potency) topical steroid. However, it is worth noting that mometasone *cream* is categorized as a class IV (medium potency) topical steroid.

Treatment

Successful treatment of LSC requires addressing 4 elements, including recognizing and treating the underlying etiology, restoring barrier function, reducing inflammation, and interrupting the itch-scratch cycle.[3]

Identifying the underlying etiology. Knowing the etiology of vulvar pruritus is a key step in resolution of the condition because LSC is driven by repetitive rubbing and scratching behaviors in response to the itch. The differential diagnosis for vulvar pruritus is broad. Evaluation and workup should be tailored to suit each unique patient presentation. A review of past medical history and full-body skin examination can identify a contributing inflammatory skin disease, such as atopic dermatitis, psoriasis, lichen planus, lichen sclerosus, or autoimmune vesiculobullous disease (pemphigus).[1,2] Careful review of products applied in the genital area can reveal an underlying irritant or allergic contact dermatitis. Scented soap or detergent commonly cause vulvar dermatitis.[1] A speculum examination may suggest inflammatory vaginitis or atrophic vaginitis (genitourinary syndrome of menopause); run off of vaginal discharge onto the vulvar skin can result in vulvar pruritus. Vaginal wet mount can diagnose vulvovaginal candidiasis, trichomonas infection, and bacterial vaginitis.[1] A skin scraping with mineral oil or potassium hydroxide can suggest scabies infestation or cutaneous dermatophyte infection, respectively.[2] Treatment of vulvar pruritus should be initiated based on diagnosis.

Restoring barrier function. The repetitive scratching and rubbing behaviors disrupt the cutaneous barrier layer and lead to stimulation of the local nerves. This creates more itch and further traumatization to the barrier. Barrier function can be restored through soaking the area, with sitz baths or damp towels. Following 20- to

30-minute soaks, a lubricant, such as petroleum jelly, should be applied to the area.3

Reducing inflammation. To reduce inflammation, topical steroids should be applied to areas of LSC.3 In severe cases, high potency topical steroids should be prescribed. Examples of high potency topical steroids include:

- clobetasol propionate 0.05%
- betamethasone dipropionate 0.05%
- halobetasol propionate 0.05%.

Ointment is the choice vehicle because it is both more potent and associated with decreased stinging sensation. High potency steroid ointment should be applied twice daily for at least 2 to 4 weeks. The transition to lower potency topical steroids, such as triamcinolone acetonide 0.1% ointment, can be made as the LSC improves.[2]

Interrupting the itch-scratch cycle. As noted above, persistent rubbing and scratching generates increased itch sensation. Thus, breaking the itch-scratch cycle is essential. Nighttime scratching can be improved with hydroxyzine. The effective dosage ranges between 25 and 75 mg and should be titrated up slowly every 5 to 7 days. Sedation is a major adverse effect of hydroxyzine, limiting the treatment of daytime itching. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram, also have been found to be effective. Over the counter, nonsedation antihistamines have not been found to be useful in breaking the itch-scratch cycle. The clinical course of LSC is chronic (as the name implies), waxing and waning, and sometimes can be challenging to treat—some patients require years-long continued follow-up and treatment.[3]

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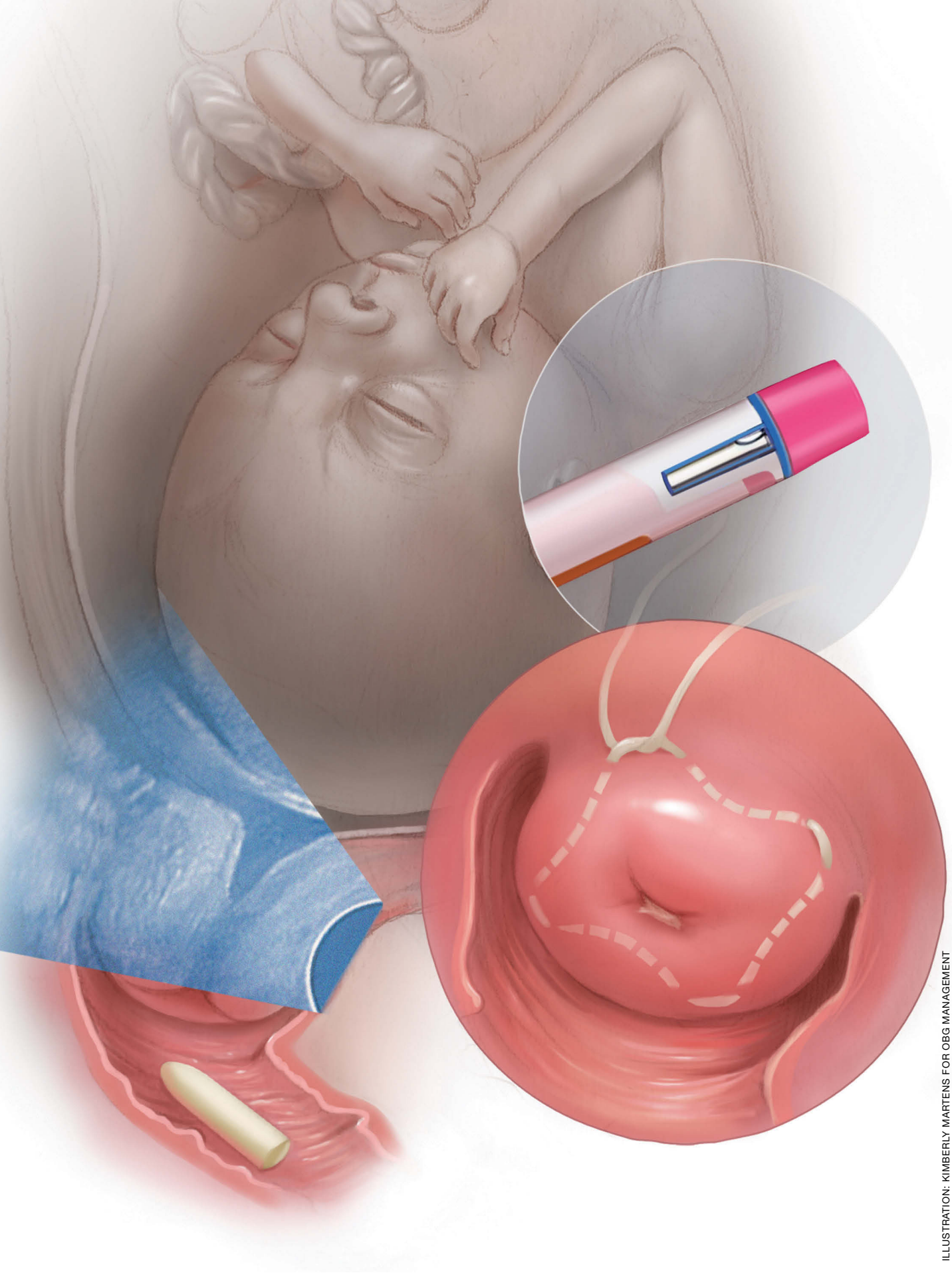

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Progesterone supplementation does not PROLONG pregnancy in women at risk for preterm birth: What do we do now?

What is the future for 17P now that a required trial for the drug's efficacy showed that its use did not reduce preterm birth, neonatal morbidity, or fetal/early infant deaths—and an FDA advisory committee recommended withdrawal of the drug's approval?

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Preterm birth (PTB) remains a significant public health concern and a major cause of newborn morbidity and mortality. In the United States, 1 in 10 babies are born preterm (< 37 weeks), and this rate has changed little in 30 years.[1]

In 2011, the US Food and Drug Administration (FDA) approved progesterone supplementation—specifically, 17 α-hydroxyprogesterone caproate (17P) injection (Makena)—to prevent recurrent PTB in women with a singleton pregnancy at high risk by virtue of a prior spontaneous PTB.[2] This was the first-ever FDA-approved drug for PTB prevention, and it was the first drug approved by the FDA for use in pregnancy in more than 15 years. The approval of 17P utilized the FDA's Subpart H Accelerated Approval Pathway, which applies to therapies that: 1) treat serious conditions with unmet need, and 2) demonstrate safety and efficacy on surrogate end points reasonably likely to predict clinical benefit.[3]

The authors report no financial relationships relevant to this article.

By voting their approval of 17P in 2011, the FDA affirmed that PTB was a serious condition with unmet need, that birth < 37 weeks was an accepted surrogate end point, and that there was compelling evidence of safety and benefit. The compelling evidence presented was a single, randomized, vehicle-controlled clinical trial conducted by the Maternal-Fetal Medicine Units (MFMU) Network, which showed significant reduction in recurrent PTB < 37 weeks (from 54.9% in the placebo group to 36.3% in the 17P group; *P*<.001; relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81).[4]

In 2017, the Society for Maternal-Fetal Medicine (SMFM) reaffirmed the use of 17P to prevent recurrent PTB and, that same year, it was estimated that 75% of eligible patients received 17P.[5,6] Importantly, Subpart H approval *requires* one or more follow-up clinical trials confirming safety and efficacy. And the FDA has the right—the responsibility—to revisit approval if such trials are either not performed or are unfavorable.

The recently published PROLONG study by Blackwell and colleagues is this required postapproval confirmatory trial conducted to verify the clinical benefit of 17P supplementation.[7]

Study design, and stunning results

PROLONG (Progestin's Role in Optimizing Neonatal Gestation) was a randomized (2:1), double-blind, vehicle-controlled, multicenter international trial (2009–2018) conducted to assess the safety and efficacy of 17P injection in 1,708 women with a singleton pregnancy and one or more prior spontaneous PTBs.[7] Women in the active treatment group (n = 1,130) received weekly intramuscular injections of 17P, while those in the control group (n = 578) received weekly injections of inert oil vehicle.

Results of the trial showed no significant reduction in the co-primary end points, which were PTB < 35 weeks (11.0% in the 17P group vs 11.5% in the placebo group; RR, 0.95;

95% CI, 0.71–1.26) and neonatal morbidity index (5.6% in the 17P group vs 5.0% in the placebo group; RR, 1.12; 95% CI, 0.68–1.61). There was no evidence of benefit for any subpopulation (geographic region, race, or other PTB risk factor). Maternal outcomes also were similar between the groups. No significant safety concerns were identified.

Important differences between MFMU and PROLONG trials

Strengths of the PROLONG trial include its randomized, placebo-controlled design, excellent follow-up rate, and use of a protocol that mirrored that of the MFMU trial. The primary limitation of PROLONG is that participants experienced a lower rate of PTB compared with those in the MFMU trial. The rate of PTB < 37 weeks was 54.9% in the control group of the MFMU trial compared with 21.9% in PROLONG.

Given the low rate of PTB in PROLONG, the study was underpowered for the co-primary outcomes. In addition, lower rates of PTB in PROLONG compared with in the MFMU trial likely reflected different patient populations.[8] Moreover, PROLONG was an international trial. Of the 1,708 participants, most were recruited in Russia (36%) and Ukraine (25%); only 23% were from the United States. By contrast, participants in the MFMU trial were recruited from US academic medical centers. Also, participants in the MFMU trial were significantly more likely to have a short cervix, to have a history of more than one PTB, and to be African American.

Discrepant trial results create clinical quandary

In October 2019, the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee voted 9-7 to withdraw approval for 17P. Committee members struggled with the conflicting data between the 2 trials and hesitated to remove a medication whose use has become standard practice. Ultimately, however, it was lack of substantial evidence of effectiveness of 17P that swayed the committee's vote. While the FDA generally follows the recommendation of an advisory committee, it is not bound to do so.

Societies' perspectives

So what are physicians and patients to do? It is possible that a small subgroup of women at extremely high risk for early PTB may benefit from 17P administration. SMFM stated: "… it is reasonable for providers to use 17-OHPC [17P] in women with a profile more representative of the very high-risk population reported in the Meis [MFMU] trial."[8] Further, the American College of Obstetricians and Gynecologists (ACOG) stated in a Practice Advisory dated October 25, 2019, that "ACOG is not changing our clinical recommendations at this time… [We] will be reviewing subsequent forthcoming analyses and will issue updated clinical guidance as appropriate."[9]

Where we stand on 17P use going forward

17P should be available to women who previously may have benefited from its use. However, 17P should not be recommended routinely to prevent recurrent spontaneous PTB in women with one prior PTB and no other risk factors. Of note, the PROLONG trial does not change recommendations for cervical length screening. Women with a history of a prior spontaneous PTB should undergo cervical length screening to identify those individuals who may benefit from an ultrasound-indicated cerclage. ●

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Managing preterm birth in those at risk: Expert strategies

Four experts share what they will do in their practice for pregnant women with a history of preterm birth should the option of using 17 α-hydroxyprogesterone caproate be withdrawn

Obstetricians face the potential practice dilemma of having withdrawn from the market the only drug approved by the US Food and Drug Administration (FDA) for the prevention of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. In the recently published PROLONG (Progestin's Role in Optimizing Neonatal Gestation) study by Blackwell and colleagues, the trial results revealed that there were no significant differences in preterm birth between women treated with 17 α-hydroxyprogesterone caproate (17P; Makena) and those who received placebo.[1] For study details and comments, see "Progesterone supplementation does not PROLONG pregnancy in women at risk for preterm birth: What do we do now?" by Michael House, MD, and Errol Norwitz, MD, PhD, MBA, on page 36. Subsequently, the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee voted 9-7 to recommend pursuit of approval withdrawal for 17P.

To assess how experienced obstetricians would manage women with previous preterm birth if 17P became unavailable, OBG MANAGEMENT conducted an informal survey. Here, 4 experts respond to the question, "What are you going to do in your practice for women with a history of a previous preterm birth if 17P is no longer an option?"

Not ready to leave behind 17P for recurrent preterm delivery

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Preterm delivery is arguably the most important problem in perinatal medicine. It occurs in 10% to 12% of all obstetric patients in the United States, and complications of prematurity account for the majority of neonatal deaths. A major risk factor for recurrent preterm delivery is a prior history of spontaneous preterm delivery, with or without preterm premature rupture of membranes. Clearly, prevention of recurrence is of paramount importance.

In the Maternal-Fetal Medicine Units (MFMU) Network trial, Meis and colleagues

The authors report no financial relationships relevant to this article.

demonstrated a 34% reduction (relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81) in the risk of recurrent preterm delivery in women who received weekly 250-mg injections of 17P (also called 17-OHPC). After publication of that trial, use of 17P became accepted practice in the United States.[2]

The PROLONG study by Blackwell and colleagues questions the value of 17P.[1] In that international trial, which included 1,708 women from 41 centers in the United States and 52 outside the United States, the authors were unable to show any significant difference in the frequency of preterm delivery < 35 weeks (11.0% in the women receiving 17P and 11.5% in women receiving placebo; RR, 0.95; 95% CI, 0.71–1.26). Even when they examined the subset of women treated at US medical centers, they could not demonstrate any significant difference in treatment outcome.

At least 2 major explanations account for the discrepancy between the MFMU and the Blackwell studies. First, the participants in the PROLONG trial were clearly not at the same increased risk for recurrent preterm delivery as those in the MFMU trial. Second, in the PROLONG trial only the minority of participants were from the United States. In fact, given the relatively low rate of recurrent preterm delivery in the PROLONG trial, the study was underpowered to detect meaningful differences in maternal outcome. Therefore, I am not ready to abandon the use of progesterone supplementation in women at risk for recurrent preterm delivery.

If the FDA removes 17P from the market, my approach with at-risk patients will be as follows:

- I will encourage all at-risk women to eliminate obvious risk factors, such as smoking, illicit drug use, and excessive physical activity.
- I will encourage optimal nutrition and appropriate weight gain.
- I will test all patients for chlamydia, gonorrhea, and bacterial vaginosis and treat women who are infected.
- After the patient completes the first trimester, I will treat her with micronized progesterone, 200 mg daily, intravaginally. I will continue this medication until 36 to 37 weeks.
- I will perform an assessment of cervical length at 16, 20, and 24 weeks' gestation. In patients with demonstrable cervical shortening, I will perform a cerclage.

FAST TRACK

Participants in PROLONG were not at the same increased risk for recurrent preterm delivery as those in the MFMU trial, and only a minority of PROLONG participants were from the United States

Rational management options for reducing risk of preterm delivery

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Most women who experience a spontaneous preterm delivery (sPTD) do not deliver prematurely in subsequent pregnancies.[3] Two recent systematic reviews, in 2014 and 2017, found an overall risk of recurrent sPTD of 20.2% and 30%, respectively.[4,5] These numbers are closer to the background event rate of 21.9% in the PROLONG trial, while only a few women have a recurrence risk of more than 50%, as in the Meis MFMU trial.[1,2] A public health recommendation cannot be made for an intervention that is expected to work only in rare cases and fail in a majority of cases. Therefore, 17P is no longer a viable option for preventing recurrence in pregnant

women with a history of sPTD, with only rare possible exceptions.

What evidence-based alternatives can be offered to pregnant women who had a previous sPTD?

Ultrasound assessment of cervical length has emerged as an effective prognosticator for recurrence in women with a prior sPTD, being able to predict 65.4% of sPTDs at a false-positive rate of 5%.[6,7] Furthermore, sonographic cervical length measurements identify high-risk women who may not need any intervention. It has been shown that, among women with prior sPTD who maintain a normal cervical length up to 24 weeks, more than 90% will deliver at 35 weeks or after without intervention.[8]

In the United States, interventions to reduce sPTD, once a short cervix has been identified, include vaginal progesterone supplementation and cerclage. The benefit from vaginal progesterone has been documented by an individual patient data meta-analysis, while the benefit of cerclage has been highlighted in a Cochrane Review.[9,10] The results of an adjusted indirect comparison meta-analysis suggest that both interventions are equally effective.[11] Therefore, the decision on how best to minimize the risk of recurrent sPTD must be individualized based on historical and clinical circumstances, as well as the woman's informed choice.

Based on current data, the following approach appears rational to me:

- Cervical ultrasound surveillance between 16 and 24 weeks' gestation to identify the subgroup of women at significantly increased risk of sPTD recurrence.
- With cervical length ≤ 25 mm, vaginal progesterone supplementation may be considered. Preferential consideration for progesterone may be given when lower genital tract inflammation is suspected, given the possible anti-inflammatory action of progesterone.[12,13]
- If cervical shortening progresses to 15 to 20 mm, cerclage may be considered. Waiting for a cervix < 15 mm may be unadvisable. In conditions of a very short cervix, frequently dilated, with exposure of the fetal membranes, ascending subclinical intra-amniotic infection already may be present, reducing the efficacy of cerclage. Preferential consideration for cerclage also may be given with 2 sPTDs or mid-trimester losses or with a history of a successful cerclage.

FAST TRACK

It has been shown that, among women with prior sPTD who maintain a normal cervical length up to 24 weeks, more than 90% will deliver at 35 weeks or after without intervention

Screen cervical length early, and use cerclage or vaginal progesterone as appropriate

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In patients with a history of a previous preterm birth, if 17P is no longer an option, I would revert to screening for short cervix with transvaginal ultrasound.

Screen all high-risk patients at the first prenatal visit, so as not to miss a short cervix before 16 weeks' gestation. Then, beginning at 16 weeks, screen every 2 weeks until approximately 24 weeks.

If the cervix shortens to 25 mm or less, offer cerclage or vaginal progesterone. If the cervix shortens to 20 mm or less, I would strongly support cerclage or vaginal progesterone.

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Use of 17P is still an option, for now

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FAST TRACK

Given that preterm birth is a syndrome and not a single diagnosis, it is still possible that there is a subgroup of women who may benefit from 17P

The way in which 17P was handled by the FDA is exactly the way the system is designed to work; this should be seen as a success, not a failure.

Given the urgent need for an intervention to prevent preterm birth, the lack of any alternative, and a single, well-designed randomized controlled trial that confirmed safety and suggested some benefit, the FDA approved 17P supplementation in February 2011 for a limited indication only—one or more prior unexplained sPTD—using the expedited review mechanism.[2] Under this mechanism, a follow-up clinical trial is required to confirm efficacy. This was the PROLONG trial, which failed to show any significant benefit of 17P supplementation in terms of either preterm birth prevention or neonatal outcome.[1]

In October 2019, an FDA advisory committee met again to review these and other data. After presentations from a range of stakeholders and a robust discussion, the advisory committee voted to pursue approval withdrawal of 17P due to the lack of consistent evidence of benefit (it is important to note that this was not because of safety concerns). This is exactly the way the process is designed to work.

Where does this leave physicians and patients? It is clear that progesterone supplementation is not a panacea for preterm birth prevention and is not indicated for all women at high risk, even those with one or more prior unexplained sPTDs. Given that preterm birth is a syndrome and not a single diagnosis, it is still possible that there is a subgroup of women who may benefit from this intervention. For this reason—and because there is no clear alternative and no known downside to the administration of this drug (other than cost)—physicians still may choose to discuss this option with their patients and, after counseling, patients still may choose to accept it. If in doubt, engage the "shared decision-making model"; talk to your patients. ●

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Symptoms of **postpartum depression** (PPD) can have a negative impact on mothers. If left untreated, these symptoms may persist for months or up to a year.[1]

Not an actual patient.

INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

Select IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.

Individual results may vary.

Not an actual patient.

STUDY DESIGN[2,3]

The efficacy of ZULRESSO in the treatment of PPD was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies (referred to as Studies 1 and 2) in women (18 to 45 years) with PPD who met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for a major depressive episode (*DSM-IV*) with onset of symptoms in the third trimester or within 4 weeks of delivery. Women were enrolled up to 6 months postpartum. In these studies, patients received a 60-hour continuous intravenous infusion of ZULRESSO or placebo and were then followed for 4 weeks. Study 1 (NCT02942004) included patients with severe PPD (HAM-D score ≥26), and Study 2 (NCT02942017) included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hour was evaluated in both studies (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, followed by a taper to 60 mcg/kg/hour for 4 hours and then 30 mcg/kg/hour for 4 hours). A titration to a target dosage of 60 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, then 30 mcg/kg/hour for 4 hours) was also evaluated in Study 1.

The safety of ZULRESSO was evaluated across 3 clinical trials (a Phase II study, Study 1, and Study 2) in 140 women who were exposed to ZULRESSO. The Phase II study evaluated 21 women with severe PPD, 10 of whom received a dose of 90 mcg/kg/hour of ZULRESSO. Baseline oral antidepressant use was reported for 23% of patients.

The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (Hour 60). A pre-specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30.

Select IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness: In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO, the **FIRST AND ONLY** FDA-approved treatment indicated for postpartum depression.

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

Each. Day. Matters.

RAPID AND SIGNIFICANT IMPROVEMENT OF DEPRESSIVE SYMPTOMS IN 2.5* DAYS[2]

Study 1

62.3% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=41)† vs 49.0% with placebo (n=43†; *P*=0.0252‡)

In a group of 38 patients in Study 1, a ZULRESSO titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

The recommended dosage of ZULRESSO is 90 mcg/kg/hour.
HAM-D=Hamilton Depression Rating Scale.

Study 2

64.6% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=51)† vs 53.3% with placebo (n=53†; *P*=0.0160‡)

*2.5 days=Hour 60.
†Intention to treat population.
‡Statistically significant after multiplicity adjustments.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

Warnings and precautions for ZULRESSO include: risk of excessive sedation, risk of sudden loss of consciousness, and suicidal thoughts and behaviors.

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Use in specific populations:

- Pregnancy: May cause fetal harm
- Avoid use in patients with end stage renal disease (ESRD)

Select IMPORTANT SAFETY INFORMATION

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS):
Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.

References: 1. Vliegen N, Casalin S, Luyten P. The course of postpartum depression: a review of longitudinal studies. *Harv Rev Psychiatry*. 2014;22(1):1-22. **2.** ZULRESSO Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc; 6/2019. **3.** Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.

INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness:
In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS): ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

SUICIDAL THOUGHTS AND BEHAVIORS

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm

  There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZULRESSO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
- **Lactation:** Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition
- **Pediatric Use:** The safety and effectiveness of ZULRESSO in pediatric patients have not been established
- **Renal Impairment:** No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD)

CONTROLLED SUBSTANCE

ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Zulresso™ (brexanolone) injection IV
for intravenous use 100mg/20mL

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

Sage Therapeutics™

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.

ZULRESSO™ (brexanolone) injection Ⓘⓥ, for intravenous use

Rx only

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, please see *Full Prescribing Information, including Boxed Warning, and Medication Guide.*)

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**
- **Because of these risks, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.**

1 INDICATIONS AND USAGE: ZULRESSO™ is indicated for the treatment of postpartum depression (PPD) in adults.

2 DOSAGE AND ADMINISTRATION

A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion.

Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Dilution required prior to administration.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Excessive Sedation and Sudden Loss of Consciousness In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and <1 minute of apnea while receiving two times the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour). All patients with loss of or altered state of consciousness recovered with dose interruption.

There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode.During the infusion, monitor patients for sedative effects every 2 hours during planned, non sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation.

After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate.

Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia,the infusion should not be resumed.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

5.3 Suicidal Thoughts and Behavior In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient

*ZULRESSO is not approved in pediatric patients.

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

6 ADVERSE REACTIONS The following adverse reactions are discussed in more detail in other sections of the labeling:

- Excessive Sedation and Sudden Loss of Consciousness

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

The data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction

In the pooled placebo controlled-studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo controlled-studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; two patients who had dosage interruption because of loss of consciousness did not resume the infusion.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60 hour treatment period.

Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients

	Placebo (n=107)	**Maximum dosage 60 mcg/kg/hour (n=38)**	**Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)**
Cardiac Disorders			
Tachycardia	-	-	3%
Gastrointestinal Disorders			
Diarrhea	1%	3%	2%
Dry mouth	1%	11%	3%
Dyspepsia	-	-	2%
Oropharyngeal pain	-	3%	2%
Nervous System Disorders			
Dizziness, presyncope, vertigo	7%	13%	12%
Loss of consciousness	-	5%	3%
Sedation, somnolence	6%	21%	13%
Vascular Disorders			
Flushing, hot flush	-	5%	2%

7 DRUG INTERACTIONS

7.1 CNS Depressants Concomitant use of ZULRESSO with CNS depressants (e.g., opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation.

7.2 Antidepressants In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.

Risk Summary

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and ≥3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rabbits at ≥3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively.

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with fewer live fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Decreased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

8.2 Lactation

Risk Summary

Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as ZULRESSO has low oral bioavailability (<5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.

8.4 Pediatric Use The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

8.5 Geriatric Use PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.

8.6 Hepatic Impairment Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh≥7) with no associated change in tolerability.

8.7 Renal Impairment No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 m^2), moderate (eGFR 30 to 59 mL/minute/1.73 m^2) or severe (eGFR 15 to 29 mL/minute/1.73 m^2) renal impairment.

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m^2 because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

9.2 Abuse In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (two times the maximum recommended infusion rate), and 270 mcg/kg (three times the maximum recommended infusion rate) ZULRESSO infusions over a one hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of "drug liking", "overall drug liking", "high" and "good drug effects", the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both dosages of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration.

9.3 Dependence In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation.

10 OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, two cases of accidental overdosage due to infusion pump malfunction resulted in transient loss of consciousness. Both patients regained consciousness approximately 15 minutes after discontinuation of the infusion without supportive measures. After full resolution of symptoms, both patients subsequently resumed and completed treatment. Overdosage may result in excessive sedation, including loss of consciousness and the potential for accompanying respiratory changes.

Management of Overdose

In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma. Consult a Certified Poison Control Center at **1-800-222-1222** for latest recommendations.

PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Manufactured for:
Sage Therapeutics, Inc.,
Cambridge, MA 02142 USA

Sage Therapeutics™

June 2019

SGS video series!

SGS SOCIETY OF GYNECOLOGIC SURGEONS

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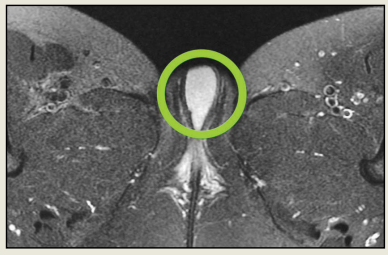
OBG MANAGEMENT

A clitoral cyst of "epidermal" proportions

ANGELA DICARLO-MEACHAM, LCDR, MC, USN; KATHERINE L. DENGLER, MAJ, MC, USA; ANDREA N. SNITCHLER, CDR, MC, USA; AND DANIEL D. GRUBER, COL, MC, USAF



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

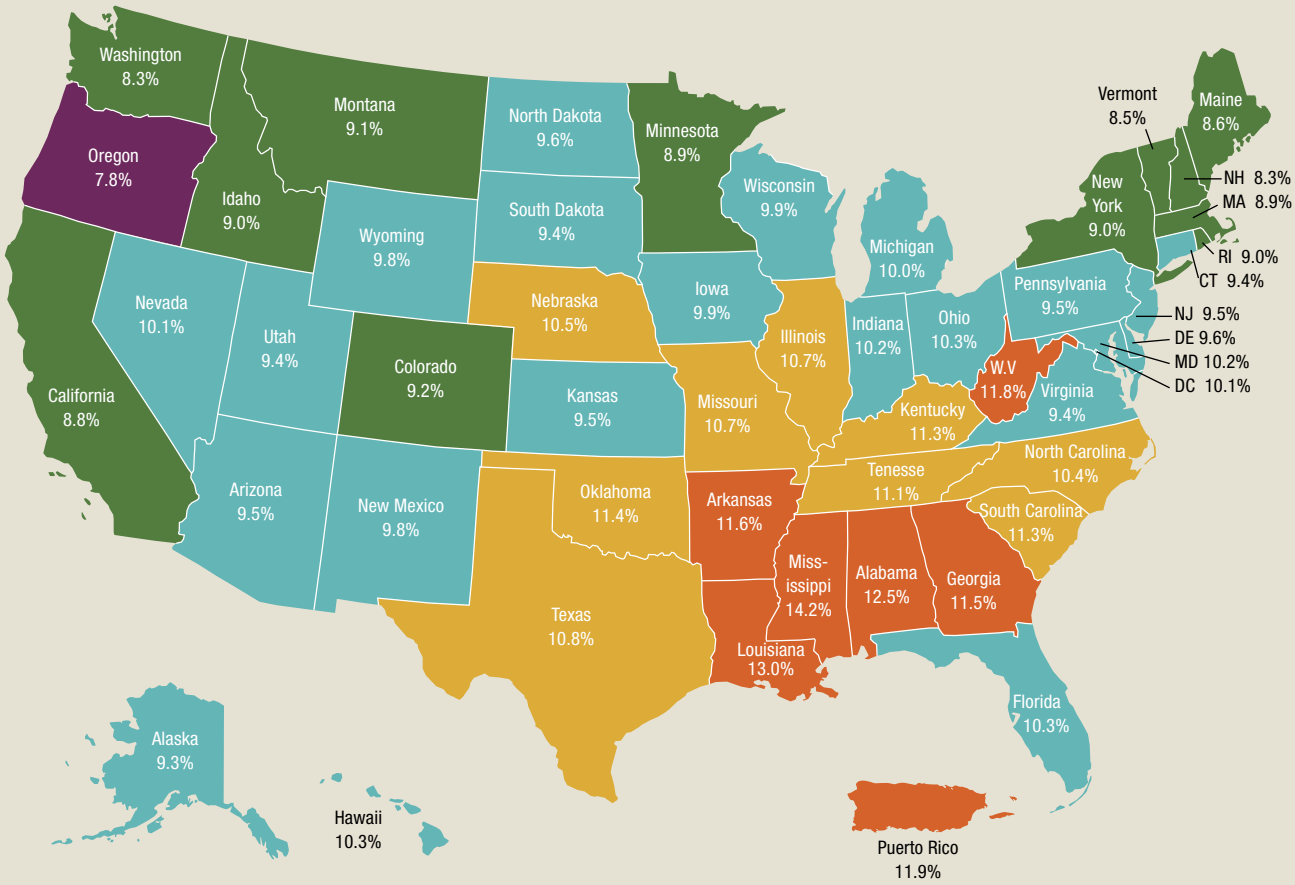
In this video, the surgeons demonstrate the management of a large clitoral cyst causing anorgasmia. They highlight the neurovascular anatomy of the clitoris and surgical techniques that avoid injury to the dorsal clitoral nerve and demonstrate a technique for reconstruction of the labia minora and clitoral hood that restores normal anatomy and provides an excellent cosmetic result. Meticulous dissection and a clear understanding of clitoral anatomy allows for safe surgical removal of clitoral masses, which may be necessary to restore sexual function.

INDEX OF ADVERTISERS

US rates of preterm birth

The preterm birth rate in the United States is 10.0%, rising slightly each year since 2015. The March of Dimes grades the current rate a C average, and it has set a goal of 8.1% for 2020. The preterm birth rates vary across each individual state, with a high of 14.2% in Mississippi and a low of 7.8% in Oregon. When aggregate preterm birth rates for 2015–2017 are calculated by race, the high is among black women at 13.6% and the low is among Asian/Pacific Islander women at 8.7%.

Preterm birth rates and grades by state



Grade	Preterm birth rate range
A, A-	≤7.7%–8.1%
B+, B, B-	8.2%–9.2%
C+, C, C-	9.3%–10.3%
D+, D, D-	10.4%–11.4%
F	≥11.5%

Source: 2019 March of Dimes Report Card. https://www.Marchofdimes.org/reportcard. Accessed November 21, 2019.

HOLOGIC®

fFN + TVUS

dramatically increases sPTB prediction

Risk of sPTB <7 days in patients with symptoms of preterm labor[1]

TVUS Alone

CL <30mm	=	~1 out of 4

TVUS + fFN

CL <30mm + **Negative fFN**	=	~1 out of 10

TVUS + fFN

CL <30mm + **Positive fFN**	=	~1 out of 2

Reference: 1. R Gomez, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. AJOG 2005; 192: 350-359.

RapidfFN®