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OBG MANAGEMENT

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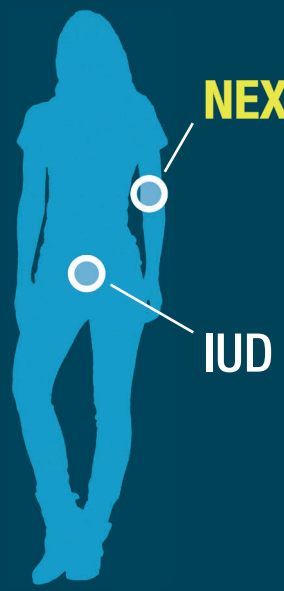


Help your patients understand both of their LARC location options[1]

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

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

US-XPL-00588 05/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

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

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

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

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

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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

MERCK

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

Nexplanon®
(etonogestrel implant) 68mg

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1810r020
Revised: 10/2018

MERCK

#1 IN READERSHIP*

OBG MANAGEMENT

mdedge.com/obgyn

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

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

FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

Imvexxy®
(estradiol vaginal inserts)
4 mcg • 10 mcg

DISCOVER A TREATMENT EXPERIENCE WITH

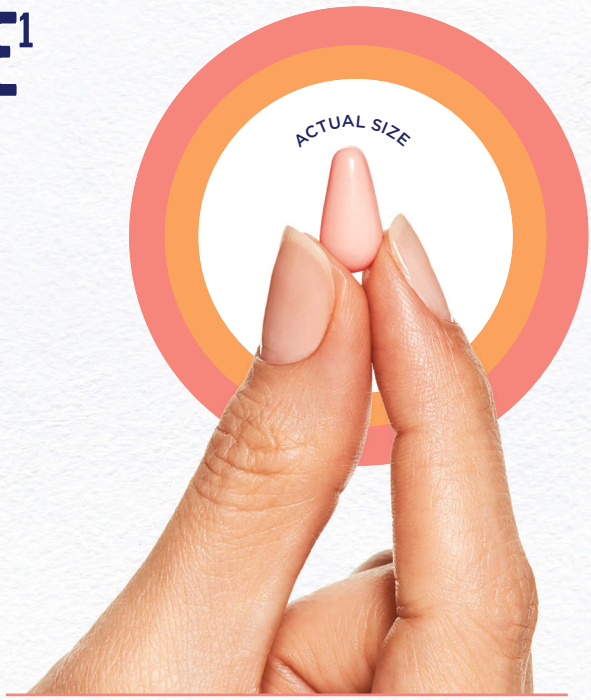
SIMPLICITY AT ITS CORE[1]

4 mcg | 10 mcg

THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES[1,2]

PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)[1,3]

MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED[1,3]



TO LEARN MORE AND REQUEST SAMPLES, VISIT IMVEXXYINFO.COM

INDICATION

IMVEXXY (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older**

CONTRAINDICATIONS

- IMVEXXY is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

- IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
- The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.
- Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS

- The most common adverse reaction with IMVEXXY (incidence ≥3 percent) and greater than placebo was headache.

Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following page.

References: 1. Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019. **2.** Data on file. Vaginal Estrogen PIs. **3.** Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause.* 2017;24(4):409-416.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use **IMVEXXY** safely and effectively. Please visit www.IMVEXXYHCP.com for Full Prescribing Information.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3) in full prescribing information].*

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].*

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].*

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].*

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg] relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].*

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2) in full prescribing information].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15) in full prescribing information].*

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (e.g., stroke and myocardial infarction (MI)) or a history of these conditions; known anaphylactic reaction or angioedema with IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY (*Pharmacokinetics [12.3] in full prescribing information*). The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] *[see Clinical Studies (14.2) in full prescribing information].*

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3) in full prescribing information].*

Other Warnings and Precautions include:

Gallbladder disease; severe hypercalcemia; visual abnormalities; elevated blood pressure; hypertriglyceridemia; hepatic impairment and/or past history of cholestati jaundice; hypothyroidism (women on thyroid replacement therapy may require higher doses of thyroid hormone); fluid retention; hypocalcemia; exacerbation of endometriosis; hereditary angioedema; exacerbation of other conditions (asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas).

ADVERSE REACTIONS

Clinical Trials Experience: In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEXXY (incidence ≥ 3 percent) and greater than placebo was headache.

Post Marketing Experience: The following adverse reactions have been identified during post-approval use of IMVEXXY 4 and 10 mcg: *Genitourinary System*: vaginal discharge.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration.

USE IN SPECIFIC POPULATIONS

IMVEXXY is not indicated for use in pregnancy, in females of reproductive potential, or in children.

Geriatric Use

An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative.

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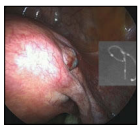

Laparoscopic techniques for Essure device removal

LINDA C. YANG, MD; LINDSAY MCALARNEN, MD, MSC; AND MARY MCKENNA, MD

See QR code on page 28

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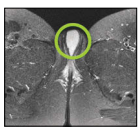

A clitoral cyst of "epidermal" proportions

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

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

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

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

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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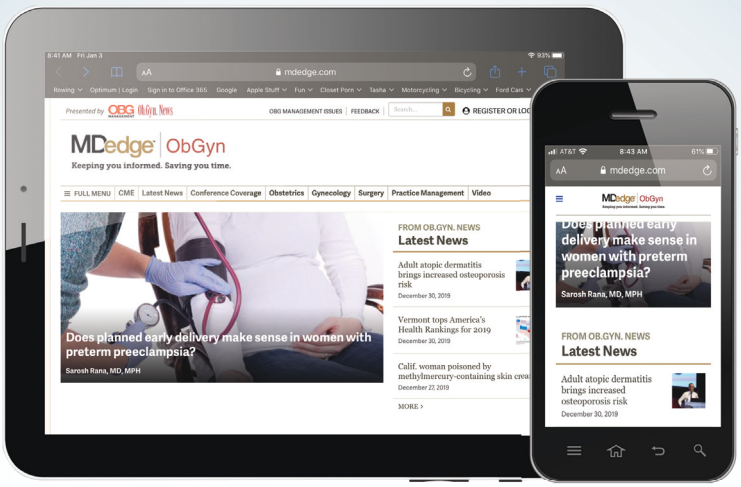

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EDITORIAL

What is optimal hormonal treatment for women with polycystic ovary syndrome?

In my practice, I commonly prescribe 3 hormone treatments for PCOS: combination estrogen-progestin contraceptive, metformin, and spironolactone. In combination, these medications rebalance the 3 system abnormalities commonly seen in women with PCOS, including reproductive, metabolic, and dermatologic dysfunction.

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Polycystic ovary syndrome (PCOS) is the triad of **oligo-ovulation** resulting in oligomenorrhea, **hyperandrogenism** and, often, **an excess number of small antral follicles** on high-resolution pelvic ultrasound. One meta-analysis reported that, in women of reproductive age, the prevalence of PCOS was 10% using the Rotterdam-European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria[1] and 6% using the National Institutes of Health 1990 diagnostic criteria.[2] (See "The PCOS trinity—3 findings in one syndrome: oligo-ovulation, hyperandrogenism, and a multifollicular ovary" on page 12.)[3]

PCOS is caused by abnormalities in 3 systems: reproductive, metabolic, and dermatologic. Reproductive abnormalities commonly observed in women with PCOS include[4]:

- an increase in pituitary secretion of luteinizing hormone (LH), resulting from both an increase in LH pulse amplitude and LH pulse frequency, suggesting a primary hypothalamic disorder
- an increase in ovarian secretion of androstenedione and testosterone due to stimulation by LH and possibly insulin
- oligo-ovulation with chronically low levels of progesterone that can result in endometrial hyperplasia
- ovulatory infertility.

Metabolic abnormalities commonly observed in women with PCOS include[5,6]:

- insulin resistance and hyperinsulinemia
- excess adipose tissue in the liver
- excess visceral fat
- elevated adipokines
- obesity
- an increased prevalence of glucose intolerance and frank diabetes.

Dermatologic abnormalities commonly observed in women with PCOS include[7]:

- facial hirsutism
- acne
- androgenetic alopecia.

Given that PCOS is caused by abnormalities in the reproductive, metabolic, and dermatologic systems, it is appropriate to consider multimodal hormonal therapy that addresses all 3 problems. In my practice, I believe that the best approach to the long-term hormonal treatment of PCOS for many women is to prescribe a combination of 3 medicines: a combination estrogen-progestin oral contraceptive (COC), an insulin sensitizer, and an antiandrogen.

The COC reduces pituitary secretion of LH, decreases ovarian androgen production, and prevents the development of endometrial hyperplasia. When taken cyclically, the COC treatment also restores regular withdrawal uterine bleeding.

An insulin sensitizer, such as metformin or pioglitazone, helps to reduce insulin resistance, glucose intolerance, and hepatic adipose content, rebalancing central metabolism. It is important to include diet and exercise in the long-term treatment of PCOS, and I always

encourage these lifestyle changes. However, my patients usually report that they have tried multiple times to restrict dietary caloric intake and increase exercise and have been unable to rebalance their metabolism with these interventions alone. Of note, in the women with PCOS and a body mass index >35 kg/m^2, bariatric surgery, such as a sleeve gastrectomy, often results in marked improvement of their PCOS.[8]

The antiandrogen spironolactone provides effective treatment for the dermatologic problems of facial hirsutism and acne. Some COCs containing the progestins drospirenone, norgestimate, and norethindrone acetate are approved by the US Food and Drug Administration for the treatment of acne. A common approach I use in practice is to prescribe a COC, plus spironolactone 100 mg daily plus metformin extended-release 750 mg to 1,500 mg daily.

Which COCs have low androgenicity?

I believe that every COC is an effective treatment for PCOS, regardless of the androgenicity of the progestin in the contraceptive. However, some dermatologists believe that combination contraceptives containing progestins with low androgenicity, such as drospirenone, norgestimate, and desogestrel, are more likely to improve acne than contraceptives with an androgenic progestin such as levonorgestrel. In one study in which 2,147 women with acne were treated by one dermatologic practice, the percentage of women reporting that a birth control pill helped to improve their acne was 66% for pills containing drospirenone, 53% for pills containing norgestimate, 44% for pills containing desogestrel, 30% for pills containing norethindrone, and 25% for pills containing levonorgestrel. In the same study, the percent of women reporting that a birth control pill made their acne worse was 3% for pills containing drospirenone, 6% for pills containing norgestimate, 2% for pills containing desogestrel, 8% for pills containing norethindrone, and 10% for pills containing levonorgestrel.[9] Given these findings, when treating a woman with PCOS, I generally prescribe a contraceptive that does not contain levonorgestrel.

Why is a spironolactone dose of 100 mg a good choice for PCOS treatment?

Spironolactone, an antiandrogen and inhibitor of 5-alpha-reductase, is commonly prescribed for the treatment of hirsutism and acne at doses ranging from 50 mg to 200 mg daily.[10,11] In my clinical experience, spironolactone at a dose of 200 mg daily commonly causes irregular and bothersome uterine bleeding while spironolactone at a dose of 100 mg daily is seldom associated with irregular bleeding. I believe that spironolactone at a dose of 100 mg daily results in superior clinical efficacy than a 50-mg daily dose, although studies report that both doses are effective in the treatment of acne and hirsutism. Spironolactone should not be prescribed to women with renal failure because it can result in severe hyperkalemia. In a study of spironolactone safety in the treatment of acne, no adverse effects on the kidney, liver, or adrenal glands were reported over 8 years of use.[12]

What insulin sensitizers are useful in rebalancing the metabolic abnormalities observed with PCOS?

Diet and exercise are superb approaches to rebalancing metabolic

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CONTINUED ON PAGE 12

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The PCOS trinity—3 findings in one syndrome: oligo-ovulation, hyperandrogenism, and a multifollicular ovary

The two approaches most commonly used to diagnose polycystic ovary syndrome (PCOS) are the 1990 National Institutes of Health (NIH) criteria and the 2003 Rotterdam-European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria (**TABLE**).[1,2] In one meta-analysis, the prevalence of PCOS in women of reproductive age was 6% and 10% when using the NIH and ESHRE/ASRM criteria, respectively.[3]

TABLE Two diagnostic systems for identifying women with PCOS

1990 NIH Definition[1]	2003 Rotterdam-ESHRE/ASRM Definition[2]
ALL REQUIRED	TWO OUT OF 3 REQUIRED
Hyperandrogenism (physical examination or laboratory testing)	Hyperandrogenism (physical examination or laboratory testing)
Oligo-ovulation, typically manifested as oligomenorrhea	Oligo-ovulation, typically manifested as oligomenorrhea
Exclude other hyperandrogenic disorders, including: nonclassical adrenal hyperplasia, ovarian tumors, Cushing syndrome, and hyperprolactinemia	Multifollicular morphology on ultrasonography (presence of ≥ 12 follicles in each ovary measuring 2 to 9 mm in diameter) or increased ovarian volume (>10 mL)

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abnormalities, but for many of my patients they are insufficient and treatment with an insulin sensitizer is warranted. The most commonly utilized insulin sensitizer for the treatment of PCOS is metformin because it is very inexpensive and has a low risk of serious adverse effects such as lactic acidosis. Metformin increases peripheral glucose uptake and reduces gastrointestinal glucose absorption. Insulin sensitizers also decrease visceral fat, a major source of adipokines. One major disadvantage of metformin is that at doses in the range of 1,500 mg to 2,250 mg it often causes gastrointestinal adverse effects such as borborygmi, nausea, abdominal discomfort, and loose stools.

Thiazolidinediones, including pioglitazone, have been reported to be effective in rebalancing central metabolism in women with PCOS. Pioglitazone carries a black box warning of an increased risk of congestive heart failure and nonfatal myocardial infarction. Pioglitazone is also associated with a risk of hepatotoxicity. However, at the pioglitazone dose commonly used in the treatment of PCOS (7.5 mg daily), these serious adverse effects are rare. In practice, I initiate metformin at a dose of 750 mg daily using the extended-release formulation. I increase the metformin dose to 1,500 mg daily if the patient has no bothersome gastrointestinal symptoms on the lower dose. If the patient cannot tolerate metformin treatment because of adverse effects, I will use pioglitazone 7.5 mg daily.

Treatment of PCOS in women who are carriers of the Factor V Leiden mutation

The Factor V Leiden allele is associated with an increased risk of venous thromboembolism. Estrogen-progestin contraception is contraindicated in women with the Factor V Leiden mutation. The prevalence of this mutation varies by race and ethnicity. It is present in about 5% of white, 2% of Hispanic, 1% of black, 1% of Native American, and 0.5% of Asian women. In women with PCOS who are known to be carriers of the mutation, dual therapy with metformin and spironolactone is highly effective.[13-15] For these women I also offer a levonorgestrel IUD to provide contraception and reduce the risk of endometrial hyperplasia.

Combination triple medication treatment of PCOS

Optimal treatment of the reproductive, metabolic, and dermatologic problems associated with PCOS requires multimodal medications including an estrogen-progestin contraceptive, an antiandrogen, and an insulin sensitizer. In my practice, I initiate treatment of PCOS by

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Can the office visit interval for routine pessary care be extended safely?

Yes, according to results of a randomized trial of 130 pessary users in which a 24-week pessary care visit was found to be noninferior to a routine care visit every 12 weeks. As most participants used vaginal estrogen, the findings may not apply to pessary users who do not use vaginal estrogen.

Propst K, Mellen C, O'Sullivan DM, et al. Timing of office-based pessary care: a randomized controlled trial. Obstet Gynecol. 2019 Dec 5. Doi: 10.1097/AOG.0000000000003580.

EXPERT COMMENTARY

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

Vaginal pessaries are a common and effective approach for managing pelvic organ prolapse (POP) as well as stress urinary incontinence (SUI). Vaginal mucosal erosions, however, may complicate pessary use. The risk for erosions may be associated with the frequency of pessary change, which involves removing the pessary, washing it, and replacing it in the vagina. Existing data do not address the frequency of pessary change. Recently, however, investigators conducted a randomized noninferiority trial to evaluate the effect of pessary visit intervals on the development of vaginal epithelial abnormalities.

Dr. Kaunitz reports receiving grant or research support from Endoceutics and Mithra, and being a consultant to AMAG, Mithra, and Pfizer.

Details of the study

At a single US hospital, Propst and colleagues randomly assigned women who used pessaries for POP, SUI, or both to routine pessary care (offices visits every 12 weeks) or to extended interval pessary care (office visits every 24 weeks). The women used ring, incontinence dish, or Gelhorn pessaries, did not change their pessaries on their own, and had no vaginal mucosal abnormalities.

A total of 130 women were randomly assigned, 64 to the routine care group and 66 to the extended interval care group. The mean age was 79 years and 90% were white, 4.6% were black, and 4% were Hispanic. Approximately 74% of the women used vaginal estrogen.

The primary outcome was the rate of vaginal epithelial abnormalities, including epithelial breaks or erosions. The predetermined noninferiority margin was set at 7.5%.

Results. At the 48-week follow-up, the rate of epithelial erosion was 7.4% in the routine care group and 1.7% in the extended interval care group, thus meeting the prespecified criteria for noninferiority of extended interval pessary care.

Women in each care group reported a similar amount of bothersome vaginal discharge. This was reported on a 5-point scale, with higher numbers indicating greater degree of bother. The mean scores were

FAST TRACK

At 48 weeks, the rate of vaginal epithelial erosion was 7.4% in the 12-week routine care group and 1.7% in the 24-week extended interval care group; thus, extended interval pessary care met the trial's prespecified criteria for noninferiority

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Many women change their pessary at home as often as weekly or daily. For women who rely on office visits for pessary care, however, the trial by Propst and colleagues provides good quality evidence that pessaries can be changed as infrequently as every 24 weeks without compromising outcomes. An important limitation of these data is that since most study participants used vaginal estrogen, the findings may not apply to pessary use among women who do not use vaginal estrogen.

ANDREW M. KAUNITZ, MD, NCMP

1.39 in the routine care group and 1.34 in the extended interval care group. No other pessary-related adverse events occurred in either care group.

Study strengths and limitations

This trial provides good evidence that the timing of office pessary care can be extended to 24 weeks without compromising outcomes. However, since nearly three-quarters of the study participants used vaginal estrogen, the results may not be applicable to pessary users who do not use vaginal estrogen. ●

EDITORIAL

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offering patients 3 medications: a COC, spironolactone 100 mg daily, and metformin extended-release formulation 750 mg daily. Some patients elect dual medication therapy (COC plus spironolactone or COC plus metformin), but many patients select treatment with all 3 medications. Although triple medication treatment of PCOS has not been tested in large randomized clinical trials, small trials report that triple medication treatment produces optimal improvement in the reproductive, metabolic, and dermatologic problems associated with PCOS.[16-18] ●

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

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Expert review of recent ObGyn essentials: the future of 17-OHPC for recurrent preterm birth, preventing early-onset group B strep disease in newborns, and updated management approaches for gestational and chronic hypertension in pregnancy

Attributed to the ancient Greek philosopher Heraclitus, and often quoted in contemporary times, is the expression "the only constant is change." This sentiment rings true for the field of obstetrics this past year, as several bread-and-butter guidelines for managing common obstetric conditions were either challenged or altered.

The publication of the PROLONG trial called into question the use of intramuscular progesterone for the prevention of preterm birth. Prophylaxis guidelines for group B streptococcal disease were updated, including several significant clinical practice changes. Finally, there was a comprehensive overhaul of the guidelines for hypertensive disorders of pregnancy, which replaced a landmark Task Force document from the American College of Obstetricians and Gynecologists (ACOG) that was published only a few years ago.

Change is constant, and in obstetrics it is vital to keep up with the changing guidelines that result as new data become available for digestion and implementation into everyday clinical practice.

IN THIS ARTICLE

Results from the PROLONG trial may shake up treatment options for recurrent preterm birth

Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial. Am J Perinatol. 2019. doi: 10.1055/s-0039-3400227.

The drug 17 α-hydroxyprogesterone caproate (17-OHPC, or 17P; Makena) was approved by the US Food and Drug Administration (FDA) in 2011 for the prevention of spontaneous preterm birth (PTB) in women with a singleton pregnancy and a history of singleton spontaneous PTB. The results of the trial by Meis and colleagues of 17-OHPC played a major role in achieving that approval, as it demonstrated a 34% reduction in recurrent PTB and a reduction in some neonatal morbidities.[1] Following the drug's approval, both ACOG and the Society for Maternal-Fetal

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Medicine (SMFM) published guidelines recommending progesterone therapy, including 17-OHPC, for the prevention of recurrent spontaneous PTB.[2]

The FDA approval of 17-OHPC was granted under an accelerated conditional pathway that required a confirmatory trial evaluating efficacy, safety, and long-term infant follow-up to be performed by the sponsor. That trial, Progestin's Role in Optimizing Neonatal Gestation (PROLONG), was started in 2009, and its results were published on October 25, 2019.[3]

Design of the trial

PROLONG was a multicenter (93 sites), randomized, placebo-controlled, double-blind study conducted in 9 countries (23% of participants were in the United States, 60% were in Russia and Ukraine). The co-primary outcome was PTB < 35 weeks and a composite neonatal morbidity and mortality index. The primary safety outcome was fetal/early infant death.

The study was designed to have 98% power to detect a 30% reduction in PTB < 35 weeks, and 90% power to detect a 35% reduction in the neonatal composite index. It included 1,708 participants (1,130 were treated with 17-OHPC, and 578 received placebo).

Trial outcomes. There was no difference in PTB < 35 weeks between the 17-OHPC and the placebo groups (11.0% vs 11.5%; relative risk [RR], 0.95; 95% confidence interval [CI], 0.71–1.26). There was no difference in PTB < 32 or < 37 weeks.

The study revealed also that there was no difference between groups in the neonatal composite index (5.6% for 17-OHPC vs 5.0% for placebo; RR, 1.12; 95% CI, 0.68–1.61). In addition, there was no difference in fetal/early infant death between the 17-OHPC and placebo groups (1.7% vs 1.9%; RR, 0.87; 95% CI, 0.4–1.81).

Conclusions. The trial investigators concluded that 17-OHPC did not demonstrate a reduction in recurrent PTB and did not decrease neonatal morbidity.

FAST TRACK

The PROLONG trial investigators concluded that 17-OHPC did not demonstrate a reduction in recurrent PTB and did not decrease neonatal morbidity

Study limitations included underpowering and selection bias

The investigators noted that the PTB rate in PROLONG was unexpectedly almost 50% lower than that in the Meis trial, and that therefore the PROLONG trial was underpowered to assess the primary outcomes.

Further, the study populations of the 2 trials were very different: The Meis trial included women at higher baseline risk for PTB (> 1 prior PTB and at least 1 other risk factor for PTB). Additionally, while the PROLONG trial included mostly white (90%), married (90%), nonsmoking women (8% smoked), the Meis trial population was 59% black and 50% married, and 20% were smokers.

The availability and common use of 17-OHPC in the United States likely led to a selection bias for the PROLONG trial population, as the highest-risk patients were most likely already receiving treatment and were therefore excluded from the PROLONG trial.

Society, and FDA, responses to the new data

The results of the PROLONG trial call into question what has become standard practice for patients with a history of spontaneous PTB in the United States. While the safety profile of 17-OHPC has not been cited as a concern, whether or not the drug should be used at all has—as has its current FDA-approved status.

In response to the publication of the PROLONG trial results, ACOG released a Practice Advisory that acknowledged the study's findings but did not alter the current recommendations to continue to offer progesterone for the prevention of preterm birth, upholding ACOG's current Practice Bulletin guidance.[2,4] Additional considerations for offering 17-OHPC use include the patients' preferences, available resources, and the setting for the intervention.

SMFM's response was more specific, stating that it is reasonable to continue to use 17-OHPC in high-risk patient populations consistent with those in the Meis trial.[5] In

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Indication

Paragard is a copper-containing IUS (intrauterine system) indicated for the prevention of pregnancy for up to 10 years.

Important Safety Information

- Paragard must not be used by women who had a post-pregnancy or post-abortion uterine infection in the past 3 months; have cancer of the uterus or cervix; acute pelvic inflammatory disease (PID); an infection of the cervix; an allergy to any component (including copper); or Wilson's disease.
- If a woman misses her period, she must be promptly evaluated for ectopic pregnancy.
- Possible serious complications that have been associated with IUSs are PID, embedment, perforation of the uterus, and expulsion.
- Paragard must not be used by pregnant women as this can be life threatening and may result in loss of pregnancy or infertility.
- Menstrual cycles may become heavier and longer with intermenstrual spotting. Bleeding may be heavier than usual at first.
- **Paragard does not protect against HIV or STIs.**

See next page for Brief Summary of Full Prescribing Information.

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR Paragard® T 380A Intrauterine Copper Contraceptive
See package insert for full prescribing information

INDICATIONS AND USAGE
Paragard is indicated for prevention of pregnancy in females of reproductive potential for up to 10 years.

CONTRAINDICATIONS
The use of Paragard is contraindicated when one or more of the following conditions exist:
- Pregnancy or suspicion of pregnancy
- Abnormalities of the uterus resulting in distortion of the uterine cavity
- Acute pelvic inflammatory disease (PID)
- Postpartum endometritis or postabortal endometritis in the past 3 months
- Known or suspected uterine or cervical malignancy
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis or other lower genital tract infection
- Conditions associated with increased susceptibility to pelvic infections
- Wilson's disease
- A previously placed IUD or IUS that has not been removed
- Hypersensitivity to any component of Paragard including copper or any of the trace elements present in the copper component of Paragard

WARNINGS AND PRECAUTIONS
Ectopic Pregnancy
Evaluate for possible ectopic pregnancy in any female who becomes pregnant while using Paragard because a pregnancy that occurs with Paragard in place is more likely to be ectopic than a pregnancy in the general population. However, because Paragard prevents most pregnancies, females who use Paragard have a lower risk of an ectopic pregnancy than sexually active females who do not use any contraception.

The incidence of ectopic pregnancy in the clinical trials with Paragard (which excluded females with a previous history of ectopic pregnancy) was approximately 0.06%. Ectopic pregnancy may require surgery and may result in loss of fertility.

Risks with Intrauterine Pregnancy
If intrauterine pregnancy occurs with Paragard in place and the strings are visible or can be retrieved from the cervical canal, remove Paragard because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of Paragard may also result in spontaneous abortion. In the event of an intrauterine pregnancy with Paragard, consider the following:

Septic Abortion
In females becoming pregnant with an intrauterine system (IUS), including Paragard in place, septic abortion with septicemia, septic shock, and death may occur. Septic abortion typically requires hospitalization and treatment with intravenous antibiotics. Septic abortion may result in spontaneous abortion or a medical indication for pregnancy termination. A hysterectomy may be required if severe infection of the uterus occurs, which will result in permanent infertility.

Continuation of Pregnancy
If a female becomes pregnant with Paragard in place and if Paragard cannot be removed or the female chooses not to have it removed, warn her that failure to remove Paragard increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Prenatal care should include counseling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid, or any other symptom that suggests complications of the pregnancy.

Sepsis
Severe infection or sepsis, including Group A Streptococcal Sepsis (GAS), have been reported following insertion of IUSs, including Paragard. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of Paragard is essential in order to minimize serious infections such as GAS.

Pelvic Inflammatory Disease and Endometritis
Insertion of Paragard is contraindicated in the presence of known or suspected Pelvic Inflammatory Disease (PID) or endometritis. IUSs, including Paragard, have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. In the clinical trials with Paragard, the incidence of PID that resulted in the removal of Paragard was approximately 0.1%.

Counsel women who receive Paragard to notify a healthcare provider if they have complaints of lower abdominal or pelvic pain, odorous discharge, unexplained bleeding, fever, or genital lesions or sores. In such circumstances, perform a pelvic examination promptly to evaluate for possible pelvic infection. Remove Paragard in cases of recurrent PID or endometritis, or if an acute pelvic infection is severe or does not respond to treatment.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and death.

Females at Increased Risk for PID
PID or endometritis are often associated with a sexually transmitted infection (STI) and Paragard does not protect against STIs. The risk of PID or endometritis is greater for females who have multiple sexual partners, and also for females whose sexual partner(s) have multiple sexual partners. Females who have had PID or endometritis are at increased risk for a recurrence or re-infection. In particular, ascertain whether a female is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome (AIDS), intravenous drug abuse).

Asymptomatic PID
PID or endometritis may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID or Endometritis in Patients Using Paragard
Remove Paragard in cases of recurrent endometritis or PID, or if an acute pelvic infection is severe or does not respond to treatment. Prophylactic antibiotics administered at the time of insertion do not appear to lower the incidence of PID.

Promptly assess and treat any female who develops signs or symptoms of PID. Perform appropriate testing for sexually transmitted infection and initiate antibiotic therapy promptly. Paragard does not need to be removed immediately. Reassess the patient in 48-72 hours. If no clinical improvement occurs, continue antibiotics and consider removal of Paragard. If the decision is to remove Paragard, start antibiotics prior to removal to avoid the potential risk for bacterial spread resulting from the removal procedure.

Actinomycosis
Actinomycosis has been associated with IUS use, including Paragard. Symptomatic women with known actinomycosis infection should have Paragard removed and receive antibiotics. Actinomycetes can be found in the genital tract cultures in healthy women without IUSs. The significance of actinomyces-like organisms on a Papanicolaou (PAP) smear in an asymptomatic IUS user is unknown, and this finding alone does not always require IUS removal and treatment. When possible, confirm a PAP smear diagnosis with cultures.

Embedment
Partial penetration of embedment of Paragard in the myometrium can make removal difficult. In some cases, surgical removal may be necessary. Breakage of an embedded Paragard during non-surgical removal has been reported.

Perforation
Partial or total perforation of the uterine wall or cervix may occur during insertions, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. The incidence of perforation during or following Paragard insertion in clinical trials was 0.2% (13 out of 5344).

Delayed detection or removal of Paragard in cases of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal penetration, intestinal obstruction, abscesses and/or damage to adjacent organs.

A postmarketing safety study conducted in Europe (EURAS IUS) with IUSs, including copper IUSs, demonstrated an increased risk of perforation in lactating women. The risk of perforation may be increased if an IUS, such as Paragard, is inserted when the uterus is fixed, retroverted or not completely involuted during the postpartum period.

If perforation does occur, locate and remove Paragard promptly. Surgery may be required. Preoperative imaging followed by laparoscopy or laparotomy is often required to remove Paragard from the peritoneal cavity.

Expulsion
Partial or complete expulsion of Paragard has been reported, resulting in the loss of contraceptive protection. The incidence of expulsion in the clinical trials with Paragard was approximately 2.3%. Consider further diagnostic imaging, such as x-ray, to confirm expulsion if the IUS is not found in the uterus.

Paragard has been placed immediately after delivery, although the risk of expulsion may be increased when the uterus is not completely involuted at the time of insertion. Remove a partially expelled Paragard.

Wilson's Disease
Paragard may exacerbate Wilson's disease, a rare genetic disease affecting copper excretion; therefore, the use of Paragard is contraindicated in females of reproductive potential with Wilson's disease.

Bleeding Pattern Alterations
Paragard can alter the bleeding pattern and result in heavier and longer menstrual cycles with intermenstrual spotting.

In two clinical trials with Paragard, there were reports of oligomenorrhea and amenorrhea; however, a casual relationship between Paragard and these events could not be established. Menstrual changes were the most common medical reason for discontinuation of Paragard. Discontinuation rates for pain and bleeding combined were the highest in the first year of use and diminished thereafter. The percentage of females who discontinued Paragard because of bleeding problems or pain during these studies ranged from 12% in the first year to 2% in year 9. Females complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue Paragard.

Magnetic Resonance Imaging (MRI) Safety Information
Non-clinical testing has demonstrated that Paragard is MR Conditional. A patient with Paragard can be safely scanned in an MR system meeting the following conditions.
- Static magnetic field of 3.0 T or 1.5T
- Maximum spatial gradient of 4,000 gauss/cm (40T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, Paragard is expected to produce a maximum temperature rise of less than 0.58° C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the system extended less than 5mm from the implant when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

Medical Diathermy
Medical equipment that contain high level of Radio-frequency (RF) energy such as diathermy may cause health effects (by heating tissue) in females with a metal-containing IUS including Paragard. Avoid using high medical RF transmitter devices in females with Paragard.

ADVERSE REACTIONS
The following serious adverse reactions are discussed in the Warnings and Precautions:
- Ectopic pregnancy
- Intrauterine pregnancy
- Septic abortion
- Group A Streptococcal Sepsis (GAS)
- Pelvic Inflammatory Disease and Endometritis
- Embedment
- Perforation
- Expulsion
- Bleeding Pattern Alterations

DRUG INTERACTIONS
No drug-drug interaction or drug-herbal supplement interaction studies have been conducted with Paragard.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Use of Paragard is contraindicated for use in pregnant females because there is no need for pregnancy prevention in a female who is already pregnant and Paragard may cause adverse pregnancy outcomes. If a female becomes pregnant with Paragard in place, there is an increased risk of miscarriage, sepsis, premature labor, and premature delivery. Advise the female of the potential risks if pregnancy occurs with Paragard in place.

Published studies on pregnancy outcome exposed to copper IUSs report up to 27% miscarriage when the IUS was removed compared to 77% miscarriage when the IUSs remained in the uterus. Studies on Paragard and birth defects have not been conducted.

Lactation
Risk Summary
No difference has been detected in concentration of copper in human milk before and after insertion of copper IUSs, including Paragard. There is no information on the effect of copper in a breastfed child or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Paragard and any potential adverse effects on the breastfed child from Paragard.

Pediatric Use
The safety and effectiveness of Paragard have been established in females of reproductive potential. Efficacy is expected to be the same for postmenarcheal females regardless of age.

Paragard is not indicated in females before menarche.

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

This brief summary is based on the Paragard Full Prescribing Information dated September 2019. The FDA-approved Full Prescribing Information can be found on paragard.com, or call CooperSurgical, Inc. at 1-877-727-2427.

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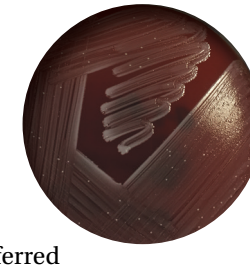
the rest of the general population at risk for recurrent PTB, SMFM recommends that, due to uncertain benefit with 17-OHPC, the high cost, patient discomfort, and increased visits should be taken into account.

Four days after the publication of the PROLONG study, the FDA Bone, Reproductive, and Urologic Drugs Advisory Committee voted 9–7 to withdraw approval for 17-OHPC.[6] In response, SMFM released a statement supporting continued access to 17-OHPC.[7] The FDA's final decision on the status of the drug is expected within the next several months from this writing.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

17-OHPC continues to be considered safe and still is recommended by both ACOG and SMFM for the prevention of recurrent preterm birth in high-risk patients. The high-risk patient population who may benefit most from this therapy is still not certain, but hopefully future studies will better delineate this. The landscape for 17-OHPC use may change dramatically if FDA approval is not upheld in the future. In my current practice, I am continuing to offer 17-OHPC to patients per the current ACOG guidelines, but I am counseling patients in a shared decision-making model regarding the findings of the PROLONG trial and the potential change in FDA approval.

ACOG updates guidance on preventing early-onset GBS disease



American College of Obstetricians and Gynecologists—Committee on Obstetric Practice. ACOG committee opinion no. 782: prevention of early-onset group B streptococcal disease in newborns. Obstet Gynecol. 2019;134:e19-e40.

Group B streptococcus (GBS) is the leading cause of newborn infection and is associated with maternal infections as well as preterm labor and stillbirth. Early-onset GBS disease occurs within 7 days of birth and is linked to vertical transmission via maternal colonization of the genitourinary or gastrointestinal tract and fetal/neonatal aspiration at birth.

Preventing early-onset GBS disease with maternal screening and intrapartum prophylaxis according to the Centers for Disease Control and Prevention (CDC) guidelines has reduced early-onset disease by 80% since the 1990s. By contrast, late-onset GBS infection, which occurs 7 days to 3 months after birth, usually is associated with horizontal maternal transmission or hospital or community infections, and it is not prevented by intrapartum treatment.

In 2018, the CDC transferred responsibility for GBS prophylaxis guidelines to ACOG and the American Academy of Pediatrics (AAP). In July 2019, ACOG released its Committee Opinion on preventing early-onset GBS disease in newborns.[8] This guidance replaces and updates the previous guidelines, with 3 notable changes.

The screening timing has changed

In the CDC's 2010 guidelines, GBS screening was recommended to start at 35 weeks' gestation. The new guidelines recommend universal vaginal-rectal screening at 36 to 37 6/7 weeks' gestation. The new timing of culture will shift the expected 5-week window in which GBS cultures are considered valid up to at least 41 weeks' gestation. The rationale for this change is that any GBS-unknown patient who previously would have been cultured under 37 weeks' would be an automatic candidate for empiric therapy and the lower rate of birth in the 35th versus the 41st week of gestation.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

ACOG's key recommendations for preventing early-onset GBS disease in newborns include:

- Universal vaginal-rectal screening for GBS should be performed at 36 to 37 6/7 weeks' gestation.
- Intrapartum antibiotic prophylaxis should be considered for low-risk patients at term with unknown GBS status and a history of GBS colonization in a prior pregnancy.
- Patients with a reported penicillin allergy require careful evaluation of the nature of their allergy, including consideration of skin testing and GBS susceptibility evaluation in order to promote the best practices for antibiotic use.
- For GBS-positive patients at high risk for penicillin anaphylaxis, vancomycin 20 mg/kg IV every 8 hours (maximum single dose, 2 g) is recommended.

FAST TRACK

Intravenous penicillin (or ampicillin) remains the antibiotic of choice for intrapartum prophylaxis against GBS due to its efficacy and specific, narrow coverage of gram-positive organisms

Identifying candidates for intrapartum treatment

The usual indications for intrapartum antibiotic prophylaxis include a GBS-positive culture at 36 weeks or beyond, GBS bacteriuria at any point in pregnancy, a prior GBS-affected child, or unknown GBS status with any of the following: < 37 weeks, rupture of membranes ≥ 18 hours or temperature ≥ 100.4°F (38°C), and a positive rapid GBS culture in labor. In addition, antibiotics now should be considered for patients at term with unknown GBS status but with a history of GBS colonization in a prior pregnancy.

This represents a major practice change for women at ≥ 37 weeks with unknown GBS status and no other traditional risk factors. The rationale for this recommendation is that women who have been positive for GBS in a prior pregnancy have a 50% chance of being colonized in the current pregnancy, and their newborns are therefore at higher risk for early-onset GBS disease.

Managing patients with penicillin allergy

Intravenous penicillin (or ampicillin) remains the antibiotic of choice for intrapartum prophylaxis against GBS due to its efficacy and specific, narrow coverage of gram-positive organisms. The updated recommendations emphasize that it is important to carefully evaluate patients with reported penicillin allergies for several reasons: determining risk of anaphylaxis and clindamycin susceptibility testing in GBS evaluations are often overlooked by obstetric providers, the need for antibiotic stewardship to reduce the development of antibiotic resistance, and clarification of allergy status for future health care needs.

Three recommendations are made:

- Laboratory requisitions for cultures should specifically note a penicillin allergy so that clindamycin susceptibility testing can be performed.
- Penicillin allergy skin testing should be considered for patients at unknown or low risk for anaphylaxis, as it is considered safe in pregnancy and most patients (80%–90%) who report a penicillin allergy are actually penicillin tolerant.
- For patients at high risk for anaphylaxis to penicillin, the recommended vancomycin dosing has been changed from 1 g IV every 12 hours to 20 mg/kg IV every 8 hours (maximum single dose, 2 g). Renal function should be assessed prior to dosing. This weight- and renal function–based dosing increased neonatal therapeutic levels in several studies of different doses.

Managing hypertension in pregnancy: New recommendations

American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 202. Gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133:e1-e25.

American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 203. Chronic hypertension in pregnancy. Obstet Gynecol. 2019;133:e26-e50.

In 2013, ACOG released "Hypertension in pregnancy," a 99-page comprehensive document developed by their Task Force on Hypertension in Pregnancy, to summarize knowledge on the subject, provide guidelines for management, and identify needed areas of research.[9] I summarized key points from that document in the 2014 "Update on Obstetrics" (*OBG Manag.* 2013;26[1]:28-36). Now, ACOG has released 2 Practice Bulletins—"Gestational hypertension and preeclampsia" and "Chronic hypertension in pregnancy"—that replace the 2013 document.[10,11] These Practice Bulletins are quite comprehensive and warrant a thorough read. Several noteworthy changes relevant to the practicing obstetrician are summarized below.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

As with ACOG's original Task Force document on hypertension, clinicians should thoroughly read these 2 Practice Bulletins on hypertension in pregnancy as there are subtle changes that affect day-to-day practice, such as the definition of hypertension prior to pregnancy, treatment guidelines, and delivery timing recommendations. As always, these are guidelines, and the obstetrician's clinical judgment and the needs of specific patient populations also must be taken into account.

Highlights of revised guidance

Expectant management vs early delivery in preeclampsia with fetal growth restriction. Fetal growth restriction, which was removed from the definition of preeclampsia with severe features in 2013, is no longer an indication for delivery in preeclampsia with severe features (previously, if the estimated fetal weight was < 5th percentile for gestational age, delivery after steroid administration was recommended). Rather, expectant management is reasonable if fetal antenatal testing, amniotic fluid, and Doppler ultrasound studies are reassuring. Abnormal umbilical artery Doppler studies continue to be an indication for earlier delivery.

Postpartum NSAID use in hypertension. The 2013 document cautioned against nonsteroidal anti-inflammatory drug (NSAID) use postpartum in women with hypertensive disorders of pregnancy because of concern for exacerbating hypertension. The updated Practice Bulletins recommend NSAIDs as the preferred choice over opioid analgesics as data have not shown these drugs to increase blood pressure, antihypertensive requirements, or other adverse events in postpartum patients with blood pressure issues.

More women will be diagnosed with chronic hypertension. Recently, the American College of Cardiology and the American Heart Association changed the definition of hypertension. Stage 1 hypertension is now defined as a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg. Treatment of stage 1 hypertension is recommended for nonpregnant adults with risk factors for current or future cardiovascular disease. The potential impact is that more women will enter pregnancy with a diagnosis of chronic hypertension, and more may be on prepregnancy antihypertensive therapy that will need to be addressed during the pregnancy.

Blood pressure goals. The target blood pressure range for pregnant women with chronic hypertension is recommended to be ≥ 120/80 mm Hg and < 160/110 mm Hg (this represents a slight change, as previously diastolic blood pressure was to be < 105 mm Hg). Postpartum blood pressure goals of < 150/100 mm Hg remain the same.

Managing acute hypertensive emergencies. Both Practice Bulletins emphasize the importance of aggressive management of acute hypertensive emergency, with options for 3 protocols: labetalol, nifedipine, and hydralazine. The goal is to administer antihypertensive therapy within 30 to 60 minutes, but administration as soon as feasibly possible after diagnosis of severe hypertension is ideal.

Timing of delivery. Recommended delivery timing in patients with chronic hypertension was slightly altered (previous recommendations included a range of 37 to 39 6/7 weeks). The lower limit of gestational age for recommended delivery timing in chronic hypertension has not changed—it remains not before

FAST TRACK

The target blood pressure range for pregnant women with chronic hypertension is recommended to be ≥ 120/80 mm Hg and < 160/110 mm Hg

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Eating for 2: Managing eating disorders in pregnancy

Clinician knowledge of complications and risks specific to disordered eating and pregnancy can affect outcomes for both mother and baby

Gianna Wilkie, MD; Leena Mittal, MD; and Nicole Smith, MD, MPH

IN THIS ARTICLE

Eating disorders affect nearly 1% of US adults,[1] and disordered eating, or unspecified eating disorder, affects at least 1% of all pregnancies.[2] Among 739 pregnant women assessed with the Eating Disorder Diagnostic scale, 7.5% of patients met criteria for an eating disorder, with 8.8% of women reporting binge eating and 2.3% of pregnant women engaging in regular compensatory behaviors. In fact, 23.4% of the study population expressed concerns about pregnancy-related weight gain and body shape.[3] Eating disorders during pregnancy are more common than previously thought, and they create unique clinical challenges for obstetric providers.

Types of eating disorders

There are 3 major types of eating disorders: anorexia nervosa, bulimia nervosa, and binge eating disorder, with significant fluidity existing between all 3 conditions.

Anorexia nervosa is a condition in which an individual believes he or she is significantly overweight despite being underweight. Patients with anorexia nervosa often restrict food intake and have compulsive rituals around eating and exercise, leading to weight loss and starvation.[4]

Bulimia nervosa is marked by intensive dieting, uncontrolled episodes of overeating, and compensatory behaviors.[4] Compensatory behaviors include self-induced vomiting; excessive exercise; and misuse of laxatives, diuretics, or other medications.

Binge eating disorder is classified as recurrent episodes of uncontrolled overeating without compensatory purging behaviors, leading to excessive weight gain.[4]

Eating disorders and pregnancy

Pregnancy can impact the course of preexisting eating disorders, and women also can develop symptoms of eating disorders for the first time during pregnancy. This is clinically significant as there are both maternal and fetal consequences to a mother's disordered eating.

The risks of anorexia nervosa include vitamin deficiencies (vitamin B12/folate), dehydration leading to renal injury and electrolyte imbalances, hypoglycemia, abnormal lipid profiles, cardiac arrhythmia, and even death. The mortality rate of patients with anorexia nervosa may approach 10%; however, death during pregnancy is quite rare.[2] Bulimia nervosa also carries the risks of protein and vitamin deficiencies, hypoglycemia and hyperglycemia, and death, with mortality estimated at 7% for those with a 5-year history

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of the illness. However, death in pregnancy due to the condition is again quite rare.[5]

Eating disorders can cause significant maternal and fetal complications during pregnancy and postpartum.

Maternal complications. When women with eating disorders become pregnant, they have increased risks of some pregnancy complications. Approximately 10% to 25% of pregnant women with eating disorders develop hyperemesis gravidarum.[6] The nausea can serve as a trigger for a woman with an eating disorder, particularly among women with a history of purging behaviors.

Cesarean delivery is more common among women with eating disorders, which may be due to preexisting fetal compromise, leading to poor tolerance of labor, or to clinicians perceiving these pregnancies as higher risk.[7]

It is well known that eating disorders are highly comorbid with depression and other psychiatric conditions. In fact, 30% to 40% of women with an eating disorder develop symptoms of postpartum depression.[8]

Fetal risks and complications. Excessive caloric restriction and dieting can lead to folate deficiency, which in turn increases the risk of neural tube defects. Such defects are more common among women with eating disorders.[9] Intrauterine growth restriction also can be a concern, most likely because of maternal malnutrition and poor maternal weight gain.[10] In addition, women with eating disorders are more likely to have a preterm delivery or experience perinatal mortality or stillbirth.[10]

Bulimia nervosa is associated with low birthweight, while anorexia nervosa is associated with the very premature birth, low birthweight, and perinatal death.[11] Eating disorders during pregnancy can have long-term psychological impacts on children, including increased likelihood of childhood hyperactivity, conduct, and adjustment disorder.[12]

FAST TRACK

The nausea of pregnancy can serve as a trigger for women with a history of purging behaviors

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How to start a conversation with a patient once you suspect an eating disorder

When a patient presents showing concerning signs or symptoms of an eating disorder, it is best to start by giving her a validated assessment tool. Normalize this questioning as routine amongst populations of obstetric patients. If concerning behaviors are identified, it is best to have an open and honest conversation with the patient about her history and current disordered eating behaviors, including restrictive, binging, or purging. It is also important to address concerns and fears about pregnancy and its associated triggers. If patients are willing to accept care, it is best to connect them with a multidisciplinary treatment team, including psychiatry, nutrition, obstetrics, and social work.

FAST TRACK

If you suspect an eating disorder, normalize the questions of a validated assessment tool (such as the SCOFF questionnaire) as routine amongst obstetric patients

Assessing patients for an eating disorder

Diagnosis of eating disorders is an interview-guided process using clinical criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*.[4] The Eating Disorder Examination is a semi-structured interview composed of 4 subsections (restraint, eating concern, shape concern, and weight concern). The interview's aim is to assess the psychopathology associated with eating disorders, and it is used in research settings rather than clinically.

Clinical diagnosis. The SCOFF questionnaire is a quick, validated tool that can be used to clinically assess for an eating disorder.[13] It is composed of 5 questions, with a positive test resulting from 2 yes answers:

1. Do you make yourself sick because you feel uncomfortably full?
2. Do you worry that you have lost control over how much you eat?
3. Have you recently lost more than one stone (14 lb) in a 3-month period?
4. Do you believe yourself to be fat when others say you are too thin?
5. Would you say that food dominates your life?

Referral. Patients for whom you have a concern for any eating disorder should be referred to a psychiatrist for formal diagnosis. Integrated multidisciplinary care of pregnant patients with eating disorders is necessary to improve maternal and fetal outcomes. Care teams should include obstetricians or maternal-fetal medicine clinicians experienced in caring for patients with eating disorders, psychiatrists, psychologists, nutritionists, and social workers. General treatment principles require an assessment for appropriate setting of intervention, which depends on presentation severity, assessment of nutritional status, treatment of psychiatric comorbidity, and psychotherapeutic intervention.

Overall management strategy

The initial treatment strategy for pregnant women with eating disorders should involve evaluating for severe illness and life-threatening complications of the specific disorder. All patients should be screened for suicidal ideation, severe malnutrition, electrolyte abnormalities, dehydration, hemodynamic instability, and cardiac arrhythmia. Patients with any of these severe features should be admitted for medical hospitalization and psychiatric evaluation.[14] Patients that are hospitalized should be watched closely for refeeding syndrome—potentially life threatening metabolic disturbances that occur when nutrition is reinstituted to patients who are severely malnourished.

Patients without severe features or acute life-threatening complications can be managed safely on an outpatient basis with close medical monitoring. Psychiatric providers should be involved to assess for treatment needs including psychotherapy and psychotropic medications. There are numerous pharmacologic options available for patients, with the use of selective serotonin reuptake inhibitors (SSRIs) most common. While SSRI use has been controversial in pregnancy in the past, the risks of untreated illness carry risk to the mother and unborn child that outweigh the small risks associated with SSRI exposure in pregnancy.[15]

Women should have established care with a nutritionist or dietician who can ensure adequate counseling regarding meal planning and multivitamin supplementation. The numerous food restrictions in pregnancy, such as avoidance of unpasteurized cheese or deli meats,

may be triggering for many patients with a history of restrictive eating.

One of the greatest difficulties for women with disordered eating in pregnancy revolves around weight gain. Many patients find the various measurements of pregnancy (maternal weight gain, fetal weight, fetal heart rate, and fundal height) triggering, which can make appropriate maternal and fetal weight gain in pregnancy very challenging. One strategy for managing this includes using fetal weight and growth as a surrogate for appropriate maternal gestational weight gain. One other strategy involves blind weights, where the woman is turned away from the scale so her weight is not disclosed to her. Patients often will not be able to achieve the expected 28 to 40 lb of pregnancy weight gain. It is best to have an open, honest conversation in early pregnancy to discuss how she would like to address weight in her pregnancy.

Postpregnancy concerns

Patients with eating disorders are at high risk of relapse in the postpartum period, even if they are able to achieve full remission in pregnancy. Rapid postpartum weight loss may be a sign of disordered eating. Postpartum depression also is a concern, and women should be followed closely for surveillance of symptoms. Finally, postpartum contraception is extremely important. The menstrual irregularities that are common among women with eating disorders along with common misconceptions regarding fertility in the postpartum period increase the risk of unplanned pregnancy.

A case of bulimia prepregnancy

A 38-year-old woman (G1) at 32 weeks' gestation presents for a routine visit. Her bulimia had been in relatively good control until the nausea of pregnancy triggered a return to purging behaviors. She reports searching her online medical record for any recording of weights, and has now started restrictive eating because a routine recent growth scan revealed the baby to be in the 80th percentile for growth. She is concerned about her mood, and thinks she may be depressed. Because her bulimia was present before pregnancy, during her pregnancy she is followed by a multidisciplinary team, including maternal-fetal medicine, perinatal psychiatry, and nutrition. At pregnancy, she elected for outpatient day program management during her pregnancy.

Remain cognizant of eating disorders

A clear surveillance plan early in the pregnancy that is developed in conjunction with the patient and her care team is crucial in improving maternal and fetal outcomes among women with an eating disorder. Clinician knowledge of complications and risks specific to disordered eating and pregnancy can affect outcomes for both mother and baby. ●

FAST TRACK

Women with a history of eating disorders should be followed postpartum for rapid weight loss and signs of depression

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COMMENTARY

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

Access to contraception is not equal. This is especially true in states with a shortage of health care providers and barriers to adequate insurance coverage.

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A new American College of Obstetricians and Gynecologists (ACOG) committee opinion[1] addresses how contraception access can be improved through over-the-counter (OTC) hormonal contraception for people of all ages—including oral contraceptive pills (OCPs), progesterone-only pills, the patch, vaginal rings, and depot medroxyprogesterone acetate (DMPA). Although ACOG endorses OTC contraception, some health care providers may be hesitant to support the increase in accessibility for a variety of reasons. We are hopeful that we address these concerns and that all clinicians can move to support ACOG's position.

Easing access to hormonal contraception is a first step

OCPs are the most widely used contraception among teens and women of reproductive age in the United States.[2] Although the Affordable Care Act (ACA) mandated health insurance coverage for contraception, many barriers continue to exist, including obtaining a prescription. Only 13 states have made it legal to obtain hormonal contraception through a pharmacist.[3] There also has been an increase in the number of telemedicine and online services that deliver contraceptives to individuals' homes. While these efforts have helped to decrease barriers to hormonal contraception access for some patients, they only reach a small segment of the population. As clinicians, we should strive to make contraception universally accessible and affordable to everyone who desires to use it. OTC provision can bring us closer to this goal.

Addressing the misconceptions about contraception

Adverse events with hormonal contraception are rarer than one may think. There are few risks associated with hormonal contraception. Venous thromboembolus (VTE) is a serious, although rare, adverse effect (AE) of hormonal contraception. The rate of VTE with combined oral contraception is estimated at 3 to 8 events per 10,000 patient-years, and VTE is even less common with progestin-only contraception (1 to 5 per 10,000 patient-years). For both types of hormonal contraception, the risk of VTE is smaller than with pregnancy, which is 5 to 20 per 10,000 patient-years.[4] There are comorbidities that increase the risk of VTE and other AEs of hormonal contraception. In the setting of OTC hormonal contraception, individuals would self-screen for contraindications in order to reduce these complications.

Patients have the aptitude to self-screen for contraindications. Studies looking at the ability of patients over the age of 18 to self-screen for contraindications to hormonal contraception have found that patients do appropriately screen themselves. In fact, they are often more conservative than a physician in avoiding hormonal contraceptive methods.[5] Patients younger than age 18 rarely have contraindications to hormonal contraception, but limited studies have shown that they too are able to successfully self-screen.[6] ACOG recommends

The authors report no financial relationships relevant to this article.

self-screening tools be provided with all OTC combined hormonal contraceptive methods to aid an individual's contraceptive choice.

Most women continue their well woman care. Some opponents to ACOG's position also have expressed concern that women who access their contraception OTC will forego their annual exam with their provider. However, studies have shown that the majority of women will continue to make their preventative health care visits.[7,8]

We need to invest in preventing unplanned pregnancy

Currently, hormonal contraception is covered by health insurance under the ACA, with some caveats. Without a prescription, patients may have to pay full price for their contraception. However, one can find generic OCPs for less than $10 per pack out of pocket. Any cost can be prohibitive to many patients; thus, transition to OTC access to contraception also should ensure limiting the cost to the patient. One possible solution to mitigate costs is to require insurance companies to cover the cost of OTC hormonal contraceptives. (See action item below.)

Reduction in unplanned pregnancies improves public health and public expense, and broadening access to effective forms of contraception is imperative in reducing unplanned pregnancies. Every $1 invested in contraception access realizes $7.09 in savings.[9] By making hormonal contraception widely available OTC, access could be improved dramatically—although pharmacist provision of hormonal contraception may be a necessary intermediate step. ACOG's most recent committee opinion encourages all reproductive health care providers to be strong advocates for this improvement in access. As women's health providers, we should work to decrease access barriers for our patients; working toward OTC contraception is a critical step in equal access to birth control methods for all of our patients.

Action items

Remember, before a pill can move to OTC access, the manufacturing (pharmaceutical) company must submit an application to the US Food and Drug Administration to obtain this status. Once submitted, the process may take 3 to 4 years to be completed. Currently, no company has submitted an OTC application and no hormonal birth control is available OTC. Resources for OTC birth control are available online (http://ocsotc.org/ and http://freethepill.org).

- Talk to your state representatives about why both OTC birth control access and direct pharmacy availability are important to increasing access and decreasing disparities in reproductive health care. Find your local and federal representatives at https://openstates.org and check the status of OCP access in your state at http://freethepill.org/statepolicies.
- Representative Ayanna Pressley (D-MA) and Senator Patty Murray (D-WA) both have introduced legislation—the Affordability is Access Act (HR 3296/S1847)—to ensure insurance coverage for OTC contraception. Call your representative and ask them to cosponsor this legislation.
- Be mindful of legislation that promotes OTC OCPs but limits access to some populations (minors) and increases cost sharing to the patient. These types of legislation can create harmful barriers to access for some of our patients.

Instant Poll

Do you agree that hormonal contraception (OCPs, progesterone-only pills, the patch, vaginal rings, and DMPA) should be offered OTC?

- Yes
- No

To weigh in, visit mdedge.com/obgyn.

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38 weeks if no antihypertensive therapy and stable, and not before 37 weeks if antihypertensive therapy and stable.

The upper limit of 39 6/7 weeks is challenged, however, because data support that induction of labor at either 38 or 39 weeks reduces the risk of severe hypertensive complications (such as superimposed preeclampsia and eclampsia) without increasing the risk of cesarean delivery. Therefore, for patients with chronic hypertension, expectant management beyond 39 weeks is cautioned, to be done only with careful consideration of risks and with close surveillance. ●

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BREAK THIS PRACTICE HABIT

We can achieve opioid-free analgesia after childbirth: Stop prescribing opioids after vaginal delivery and reduce their use after cesarean

Routine use of opioids after childbirth should be discontinued. Three practical strategies can help ObGyns reduce opioid prescriptions and adequately manage patients' pain.

Erica Holland, MD, and Julian N. Robinson, MD

CASE New mother receives unneeded opioids after CD

A house officer wrote orders for a healthy patient who had just had an uncomplicated cesarean delivery (CD). The hospital's tradition dictates orders for oxycodone plus acetaminophen tablets in addition to ibuprofen for all new mothers. At the time of the patient's discharge, the same house officer prescribed 30 tablets of oxycodone plus acetaminophen "just in case," although the patient had required only a few tablets while in the hospital on postoperative day 2 and none on the day of discharge.

Stuck in the habit

Prescribing postpartum opioids in the United States is almost habitual. Both optimizing patient satisfaction and minimizing patient phone calls may be driving this well-established pattern. Interestingly, a survey study of obstetric providers in 14 countries found that clinicians in 13 countries prescribe opioids "almost never" after vaginal delivery.[1] The United States was the 1 outlier, with providers reporting prescribing opioids "on a regular basis" after vaginal birth. Similarly, providers in 10 countries reported prescribing opioids "almost never" after CD, while those in the United States reported prescribing opioids "almost always" in this context.

Moreover, mounting data suggest that many patients do not require the quantity of opioids prescribed and that our overprescribing may be causing more harm than good.

The problem of overprescribing opioids after childbirth

Opioid analgesia has long been the mainstay of treatment for postpartum pain, which when poorly controlled is associated with the development of postpartum depression and chronic pain.[2] However, common adverse effects of opioids, including nausea, drowsiness, and dizziness, similarly can interfere with self-care and infant care. Of additional concern, a 2016 claims data study found that 1 of 300 opioid-naïve women who were prescribed opioids at discharge after CD used these medications persistently in the first year postpartum.[3]

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Many women do not use the opioids that are prescribed to them at discharge, thus making tablets available for potential diversion into the community—a commonly recognized source of opioid misuse and abuse.[4,5] In a 2018 Committee Opinion on postpartum pain management, the American College of Obstetricians and Gynecologists (ACOG) stated that "a stepwise, multimodal approach emphasizing nonopioid analgesia as first-line therapy is safe and effective for vaginal deliveries and cesarean deliveries."[6] The Committee Opinion also asserted that "opioid medication is an adjunct for patients with uncontrolled pain despite adequate first-line therapy."[6]

Despite efforts by the Centers for Disease Control and Prevention (CDC) and ACOG to improve opioid prescribing patterns after childbirth, the vast majority of women receive opioids in the hospital and at discharge not only after CD, but after vaginal delivery as well.[4,7]

Why has tradition prevailed over data, and why have we not changed?

FAST TRACK

Despite efforts by the CDC and ACOG to improve opioid prescribing patterns after childbirth, the vast majority of women receive opioids in the hospital and at discharge not only after CD, but also after vaginal delivery

Common misconceptions about reducing opioid use

Two misconceptions persist regarding reducing opioid prescriptions for postpartum pain.

Misconception #1: Patients will be in pain

Randomized controlled trials that compared nonopioid with opioid regimens in the emergency room setting and opioid use after outpatient general surgery procedures have demonstrated that pain control for patients receiving opioids was equivalent to that for patients with pain managed with nonopioid regimens.[8-10] In the obstetric setting, a survey study of 720 women who underwent CD found that higher quantities of opioid tablets prescribed at discharge were not associated with improved pain, higher satisfaction, or lower refill rates at 2 weeks postpartum.[4] However, greater quantities of opioids prescribed at the time of discharge were associated with greater opioid consumption.

Recently, several quality improvement studies implemented various interventions and successfully decreased postpartum opioid consumption without compromising pain management. One quality improvement project eliminated the routine use of opioids after CD and decreased the proportion of patients using any opioids in the hospital from 68% to 45%, with no changes in pain scores.[11] A similar study implemented an enhanced recovery after surgery (ERAS) program for women after CD; mean in-patient opioid use decreased from 10.7 to 5.4 average daily morphine equivalents, with improvement in the proportion of time that patients reported their pain as acceptable.[12]

Misconception #2: Clinicians will be overwhelmed with pages and phone calls

Providers commonly fear that decreasing opioid use will lead to an increased volume of pages and phone calls from patients requesting additional medication. However, data suggest otherwise. For example, a quality improvement study that eliminated the routine use of opioids after CD tracked the number of phone calls that were received requesting rescue opioid prescriptions after discharge.[11] Although the percentage of women discharged with opioids decreased from 90.6% to 40.3%, the requests for rescue opioid prescriptions did not change. Of 191 women, 4 requested a rescue prescription prior to the intervention compared with no women after the intervention. At the same time, according to unpublished data (Dr. Holland), satisfaction among nurses, house staff, and faculty did not change.

Similarly, a quality improvement project that implemented shared decision-making to inform the quantity of opioids prescribed at discharge demonstrated that the number of tablets prescribed decreased from 33.2 to 26.5, and there was no change in the rate of patients requesting opioid refills.[13]

Success stories: Strategies for reducing opioid use after childbirth

While overall rates of opioid prescribing after vaginal delivery and CD remain high throughout the United States, various institutions have developed successful and

reproducible strategies to reduce opioid use after childbirth both in the hospital and at discharge. We highlight 3 strategies below.

Strategy 1: ERAS initiatives

An integrated health care system in northern California studied the effects of an ERAS protocol for CD across 15 medical centers.[12] The intervention centered on 4 pillars: multimodal pain management, early mobility, optimal nutrition, and patient engagement through education. Specifically, multimodal pain management consisted of the following:

- intrathecal opioids during CD
- scheduled intravenous acetaminophen for 24 hours followed by oral acetaminophen every 6 hours
- nonsteroidal anti-inflammatory drugs (NSAIDs) every 6 hours
- oral oxycodone for breakthrough pain
- decoupling of opioid medication from nonopioids in the post-CD order set
- decoupling of opioid and nonopioid medications in the discharge order set along with a reduction from 30 to 20 tablets as the default discharge quantity.

Among 4,689 and 4,624 patients who underwent CD before and after the intervention, the daily morphine milligram equivalents (MME) consumed in the hospital decreased from 10.7 to 5.4. The percentage of women who required no opioids while in the hospital increased from 8.3% to 21.4% after ERAS implementation, while the percentage of time that patients reported acceptable pain scores increased from 82.1% to 86.4%. The average number of opioid tablets prescribed at discharge also decreased, from 37 to 26 MME.[12] (The **TABLE** shows oxycodone doses converted to MMEs.)

A similar initiative at a network of 5 hospitals in Texas showed that implementation of a "multimodal pain power plan" (which incorporated postpartum activity goals with standardized order sets) decreased opioid use after both vaginal delivery and CD.[14]

Strategy 2: Order set change to eliminate routine use of opioids

A tertiary care center in Boston, Massachusetts, implemented a quality improvement project aimed at eliminating the routine use of opioid medication after CD through an order set change.[11] The intervention consisted of the following:

- intrathecal morphine
- multimodal postoperative pain management including scheduled oral acetaminophen for 72 hours followed by as-needed oral acetaminophen, scheduled NSAIDs for 72 hours followed by as-needed NSAIDs
- no postoperative order for opioids unless the patient had a contraindication to acetaminophen or NSAIDs, had a history of opioid dependence, or underwent complex surgery
- counseling patients that opioids were available for breakthrough pain if needed. In this case, nursing staff would page the responding clinician, who would order oxycodone 5 mg every 6 hours for 6 doses.
- specific criteria for discharge quantities of opioids: if the patient required no opioids in the hospital, she received no opioids at discharge; if the patient required opioids in the hospital but none at the time of discharge, she received no more than 10 tablets of oxycodone 5 mg; if the patient required opioids at the time of discharge, she received a maximum of 20 tablets of oxycodone 5 mg.

Among 191 and 181 women undergoing CD before and after the intervention, the percentage of patients who received any opioids in the hospital decreased from 68.1% to 45.3%.[11] Similarly, the percentage of patients receiving a discharge prescription for opioids decreased from 90.6% to 40.3%, while patient pain scores and satisfaction with pain control remained unchanged.

TABLE Oxycodone doses and corresponding MMEs[16]

Oxycodone, mg	MME
5	7.5
10	15
15	22.5
20	30
25	37.5
30	45

Abbreviation: MME, morphine milligram equivalent.

FAST TRACK

After implementation of an ERAS protocol for CD, the percentage of women who required no opioids while in the hospital increased from 8.3% to 21.4%, while the percentage of time that patients reported acceptable pain scores increased from 82.1% to 86.4%

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Strategy 3: Shared decision-making tool

Another tertiary care center in Boston evaluated the effects of a shared decision-making tool on opioid discharge prescribing after CD.[15] The intervention consisted of a 10-minute clinician-facilitated session incorporating:

- education around anticipated patterns of postoperative pain
- expected outpatient opioid use after CD
- risks and benefits of opioids and nonopioids
- education around opioid disposal and access to refills.

Among the 50 women enrolled in the study, the number of oxycodone 5-mg tablets prescribed at discharge decreased from the institutional standard of 40 to 20. Ninety percent of women reported being satisfied or very satisfied with their pain control, while only 4 of 50 women required an opioid refill. A follow-up quality improvement project, which implemented the shared decision-making model along with a standardized multimodal pain management protocol, demonstrated a similar decrease in the quantity of opioids prescribed at discharge.[13]

Change is here to stay: A new culture of postpartum analgesia

The CDC continues to champion responsible opioid prescribing, while ACOG advocates for a reassessment of the way that opioids are utilized postpartum. The majority of women in the United States, however, continue to receive opioids after both vaginal delivery and CD. Consciously or not, we clinicians may be contributing to an outdated tradition that is potentially harmful both to patients and society. Reproducible strategies exist to reduce opioid use without compromising pain control or overwhelming clinicians with phone calls. It is time to embrace the change. ●

FAST TRACK

Reproducible strategies exist to reduce opioid use without compromising pain control or overwhelming clinicians with phone calls. It is time to embrace the change.

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RISKY MEDICINE, PART 1

Medical malpractice: Its evolution to today's risk of the "big verdict"

Those who practice unreasonably risky medicine are few and far between, but they drive up medical malpractice claims paid as well as insurance rates for all. A look at how we have evolved to today's medical malpractice climate.

Steven R. Smith, MS, JD, and Joseph S. Sanfilippo, MD, MBA

IN THIS ARTICLE

Medical malpractice (more formally, professional liability, but we will use the term malpractice) has been of concern to ObGyns for many years, and for good reasons. This specialty has some of the highest incidents of malpractice claims, some of the largest verdicts, and some of the highest malpractice insurance rates. We look more closely at ObGyn malpractice issues in a 3-part "What's the Verdict" series over the next few months.

In part 1, we discuss the background on malpractice and reasons why malpractice rates have been so high—including large verdicts and lawsuit-prone physicians. In the second part we will look at recent experience and developments in malpractice exposure—who is sued and why. Finally, in the third part we will consider suggestions for reducing the likelihood of a malpractice lawsuit, with a special focus on recent research regarding apologies.

Two reports of recent trials involving ObGyn care illustrate the risk of "the big verdict."[1,2] (Note that the following vignettes are drawn from actual cases but are outlines of those cases and not complete descriptions of the claims. Because the information does not come from formal court records, the facts may be inaccurate and are incomplete; they should be viewed as illustrations only.)

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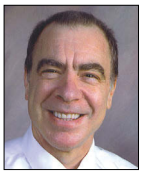

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CASE 1 Delayed delivery, $19M verdict

At 39 weeks' gestation, a woman was admitted to the hospital in spontaneous labor. Artificial rupture of membranes with clear amniotic fluid was noted. Active contractions occurred for 11 hours. Oxytocin was then initiated, and 17 minutes later, profound fetal bradycardia was detected. There was recurrent evidence of fetal distress with meconium. After a nursing staff change a second nurse restarted oxytocin for a prolonged period. The physician allowed labor to continue despite fetal distress, and performed a cesarean delivery (CD) 4.5 hours later. Five hours postdelivery the neonate was noted to

have a pneumothorax, lung damage, and respiratory failure. The infant died at 18 days of age.

The jury felt that there was negligence—failure to timely diagnose fetal distress and failure to timely perform CD, all of which resulted in a verdict for the plaintiff. The jury awarded in excess of $19 million.[1]

CASE 2 An undiagnosed tumor, $20M verdict

A patient underwent bilateral mastectomy. Following surgery, she reported pain and swelling at the surgical site for 2 years, and the defendant physician "dismissed" her complaint, refusing to evaluate it as the provider felt it was related to scar tissue. Three years after the mastectomies, the patient underwent surgical exploration and removal of 3 ribs and sternum secondary to a desmoid tumor. Surgical mesh and chest reconstruction was required, necessitating long-term opioids and

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sleeping medications that "will slow her wits, dull her senses and limit activities of daily living." Of note, discrepancies were found in the medical records maintained by the defendant. (There was, for example, no report in the record of the plaintiff's pain until late in the process.) The plaintiff based her claim on the fact that her pain and lump were neither evaluated nor discovered until it was too late.

The jury awarded $20 million. The verdict was reduced to $2 million by the court based on state statutory limits on malpractice damages.[2,3]

Medical malpractice: Evolution of a standard of care

Medical malpractice is not a modern invention. Some historians trace malpractice to the Code of Hammurabi (2030 BC), through Roman law,[4] into English common law.[5] It was sufficiently established by 1765 that the classic legal treatise of the century referred to medical malpractice.[6,7] Although medical malpractice existed for a long time, actual malpractice cases were relatively rare before the last half of the 20th century.[8]

Defensive medicine born out of necessity. The number of malpractice cases increased substantially—described as a "geometric increase"—after 1960, with a 300% rise between 1965 and 1970.[7,9] This "malpractice maelstrom of the 70s"[7] resulted in dramatic increases in malpractice insurance costs and invited the practice of defensive medicine—medically unnecessary or unjustified tests and services.[10] Although there is controversy about what is defensive medicine and what is reasonably cautious medicine, the practice may account for 3% of total health care spending.[11] Mello and others have estimated that there may be a $55 billion annual cost related to the medical malpractice system.[12]

Several malpractice crises and waves of malpractice or tort reform ensued,[13] beginning in the 1970s and extending into the 2000s.[11] Malpractice law is primarily a matter of state law, so reform essentially has been at the state level—as we will see in the second part in this series.

FAST TRACK

Medical malpractice has come to focus primarily on negligence, which is carelessness that falls below the acceptable standard of care

Defining a standard of care

Medical malpractice is the application of standard legal principles to medical practice. Those principles generally are torts (intentional torts and negligence), and sometimes contracts.[14] Eventually, medical malpractice came to focus primarily on negligence. The legal purposes of imposing negligence liability are compensation (to repay the plaintiff the costs of the harm caused by the defendant) and deterrence (to discourage careless conduct that can harm others.)

Negligence is essentially carelessness that falls below the acceptable standard of care. Negligence may arise, for example, from[15]:

- doing something (giving a drug to a patient with a known allergy to it)
- not doing something (failing to test for a possible tumor, as in the second case above)
- not giving appropriate informed consent
- failing to conduct an adequate examination
- abandoning a patient
- failing to refer a patient to a specialist (or conduct a consultation).

(In recent years, law reforms directed specifically at medical malpractice have somewhat separated medical malpractice from other tort law.)

In malpractice cases, the core question is whether the provider did (or did not) do something that a reasonably careful physician would have done. It is axiomatic that not all bad outcomes are negligent. Indeed, not all mistakes are negligent—only the mistakes that were unreasonable given all of the circumstances. In the first case above, for example, given all of the facts that preceded it, the delay of the physician for 4.5 hours after the fetal distress started was, as seen by the jury, not just a mistake but an unreasonable mistake. Hence, it was negligent. In the second case, the failure to investigate the pain and swelling in the surgical site for 2 years (or failure to refer the patient to another physician) was seen by the jury as an unreasonable mistake—one that would not have been made by a reasonably careful practitioner.

The big verdict

Everyone—every professional providing service, every manufacturer, every driver—eventually will make an unreasonable mistake (ie, commit negligence). If that negligence results in harming someone else, our standard legal response is that the negligent person should be financially responsible for the harm to the other. So, a driver who fails to stop at a red light and hits another car is responsible for those damages. But the damages may vary—perhaps a banged-up fender, or, in another instance, with the same negligence, perhaps terrible personal injuries that will disable the other driver for life. Thus, the damages can vary for the same level of carelessness. The "big verdict" may therefore fall on someone who was not especially careless.

Big verdicts often involve long-term care. The opening case vignettes illustrate a concern of medical malpractice generally—especially for ObGyn practice—the very high verdict. Very high verdicts generally reflect catastrophic damages that will continue for a long time. Bixenstine and colleagues found, for example, that catastrophic payouts often involved "patient age less than 1 year, quadriplegia, brain damage, or lifelong care."[16] In the case of serious injuries during delivery, for example, the harm to the child may last a lifetime and require years and years of intensive medical services.

Million-dollar-plus payouts are on the rise. The percentage of paid claims (through settlement or trial) that are above $1 million is increasing. These million-dollar cases represent 36% of the total *dollars* paid in ObGyn malpractice claims, even though they represent only 8% of the number of *claims* paid.[16] The increase in the big verdict cases (above $1 million) suggests that ObGyn practitioners should consider their malpractice policy limits—a million dollars may not be enough.

In big verdict cases, the great harm to the plaintiff is often combined with facts that produce extraordinary sympathy for the plaintiff. Sometimes there is decidedly unsympathetic conduct by the defendant as well. In the second case, for example, the problems with the medical record may have suggested to the jury that the doctor was either trying to hide something or did not care enough about the patient even to note a serious complaint. In a case we reviewed in an earlier "What's the Verdict" column, a physician left the room for several minutes during a critical time—to take a call from a stockbroker.[16-18]

The big verdict does not necessarily suggest that the defendant was especially or grossly negligent.[16] It was a bad injury that occurred, for instance. On the other hand, the physician with several malpractice judgments may suggest that this is a problem physician.

Physicians facing multiple lawsuits are the exceptions

A number of studies have demonstrated that only a small proportion of physicians are responsible for a disproportionate number of paid medical malpractice claims. ("Paid claims" are those in which the plaintiff receives money from the doctor's insurance. "Filed claims" are all malpractice lawsuits filed. Many claims are filed, but few are paid.)

ObGyn has high number of paid claims and high risk of claim payment recurrence. Studdert and colleagues found that the probability of future paid malpractice climbed with each past paid claim.[19] They also found that 1% of physicians accounted for 32% of all paid claims. The number of paid claims varied by specialty—obstetrics and gynecology accounted for the second largest number of paid claims (13%). The risk of recurrence (more than one paid claim) was highest among 4 surgical specialties and ObGyns (about double the recurrence rate in these specialties compared with internal medicine).[19]

A minority of physicians responsible for lion share of paid claims. Black and colleagues followed up the Studdert study. Although there were some differences in what they found, the results were very similar.[20] For example, they found that having even a single prior paid claim strongly predicted future claims over the next 5 years. They also found that some "outlier" physicians with multiple paid claims

FAST TRACK

"Big verdicts"—paid claims, through settlement or trial, that are above $1 million—are on the rise and represent 36% of the total dollars paid in ObGyn malpractice claims

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"are responsible for a significant share of paid claims." They specifically found that, even for physicians in high-risk specialties in high-risk states, "bad luck is highly unlikely to explain" multiple claims within 5 years.

Both of the studies just mentioned relied on the National Practitioner Data Bank for information about paid claims. This source has some limitations in capturing claims or payments made by hospitals or other institutions for the actions of its agent-physicians. Some of these limitations were resolved in another recent study that looked at Indiana state insurance and licensing discipline records (over a 41-year period).[21] Not surprisingly, this study found that claims paid increase with more severe licensure discipline. On the other hand, although, the "frequent fliers" in terms of malpractice claims made and paid could be identified as a "small number of repeat defendants," these physicians were not routinely disciplined by the state medical board. This was only a single state study, of course, but it also found that a few physicians accounted for a significant number of the claims. The state board was not taking licensing action against this small group, however.

Should the few bad apples be picked from the orchard?

Collectively, these studies are fairly overwhelming in demonstrating that there are some physicians who are "prone" to malpractice claims (for whom all physicians in the specialty are probably paying higher malpractice rates), but who do not attract the attention of licensing agencies for careful examination. In addition to its self-interest in eliminating physicians prone to malpractice claims and payments, the obligation of professions to protect the public interest suggests that state boards should be more aggressive in pursuing those physicians practicing risky medicine. ●

This medical malpractice series will continue next month with a look at how to reduce malpractice exposure.

FAST TRACK

In a single state study, the medical board did not routinely discipline the few physicians who accounted for a significant number of the malpractice claims paid

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Considerations on the mode of delivery for pregnant women with hepatitis C infection

While the mode of delivery's effect on vertical transmission rates of HCV infection is debated, 2 select groups of patients with HCV infection may benefit from cesarean delivery. The authors offer pertinent study data that can help guide decision making.

Morgan Brazel, BA, and Patrick Duff, MD

CASE Pregnant woman with chronic opioid use and HIV, recently diagnosed with HCV

A 34-year-old primigravid woman at 35 weeks' gestation has a history of chronic opioid use. She previously was diagnosed with human immunodeficiency virus (HIV) infection and has been treated with a 3-drug combination antiretroviral regimen. Her most recent HIV viral load was 750 copies/mL. Three weeks ago, she tested positive for hepatitis C virus (HCV) infection. Liver function tests showed mild elevations in transaminase levels. The viral genotype is 1, and the viral load is 2.6 million copies/mL.

How should this patient be delivered? Should she be encouraged to breastfeed her neonate?

The scope of HCV infection

Hepatitis C virus is a positive-sense, enveloped, single-stranded RNA virus that belongs to the Flaviviridae family.[1] There are 7 confirmed major genotypes of HCV and 67 confirmed subtypes.[2] HCV possesses several important virulence factors. First, the virus's replication is prone to frequent mutations because its RNA polymerase lacks proofreading activity, resulting in significant genetic diversity. The great degree of heterogeneity among HCV leads to high antigenic variability, which is one of the main reasons there is not yet a vaccine for HCV.[3] Additionally, HCV's genomic plasticity plays a role in the emergence of drug-resistant variants.[4]

Virus transmission. Worldwide, approximately 130 to 170 million people are infected with HCV.[5] HCV infections are caused primarily by exposure to infected blood, through sharing needles for intravenous drug injection and through receiving a blood transfusion.[6] Other routes of transmission include exposure through sexual contact, occupational injury, and perinatal acquisition.

The risk of acquiring HCV varies for each of these transmission mechanisms. Blood transfusion is no longer a common mechanism of transmission in places where blood donations are screened for HCV antibodies and viral RNA. Additionally, unintentional needle-stick injury is the only occupational risk factor associated with HCV infection, and health care workers do not have a greater prevalence of HCV than the general population. Moreover, sexual transmission is not a

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TABLE 1 **World Health Organization treatment recommendations for chronic HCV infection in adults without cirrhosis**[18,19]

Drugs	Dose	Duration of treatment	Rate of SVR	Total cost for a single course of therapy
Glecaprevir/pibrentasvir	300 mg/120 mg	8 weeks	> 94% for all genotypes	$40,000
Sofosbuvir/daclatasvir	400 mg/60 mg	12 weeks	> 92% for genotypes 1, 2, 3, and 4; 88% for genotype 5; 94% for genotype 6	$91,000
Sofosbuvir/velpatasvir	400 mg/100 mg	12 weeks	> 96% for all genotypes except genotype 3; 89% for genotype 3	$60,000

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

particularly efficient mechanism for spread of HCV.[7] Therefore, unsafe intravenous injections are now the leading cause of HCV infection.[6]

Consequences of HCV infection. Once infected with HCV, about 25% of people spontaneously clear the virus and approximately 75% progress to chronic HCV infection.[5] The consequences of long-term infection with HCV include end-stage liver disease, cirrhosis, and hepatocellular carcinoma.

Approximately 30% of people infected with HCV will develop cirrhosis and another 2% will develop hepatocellular carcinoma.[8] Liver transplant is the only treatment option for patients with decompensated cirrhosis or hepatocellular carcinoma as a result of HCV infection. Currently, HCV infection is the leading indication for liver transplant in the United States.[9]

FAST TRACK

Risk factors for HCV transmission from mother to child include HIV co-infection, internal fetal monitoring, and longer duration of membrane rupture

Risk of perinatal HCV transmission

Approximately 1% to 8% of pregnant women worldwide are infected with HCV.[10] In the United States, 1% to 2.5% of pregnant women are infected.[11] Of these, about 6% transmit the infection to their offspring. The risk of HCV vertical transmission increases to about 11% if the mother is co-infected with HIV.[12] Vertical transmission is the primary method by which children become infected with HCV.[13]

Several risk factors increase the likelihood of HCV transmission from mother to child, including HIV co-infection, internal fetal monitoring, and longer duration of membrane rupture.[14] The effect that mode of delivery has on vertical transmission rates, however, is still debated, and a Cochrane Review found that there were no randomized controlled trials assessing the effect of mode of delivery on mother-to-infant HCV transmission.[15]

Serology and genotyping used in diagnosis

The serological enzyme immunoassay is the first test used in screening for HCV infection. Currently, third- and fourth-generation enzyme immunoassays are used in the United States.[16] However, even these newer serological assays cannot consistently and precisely distinguish between acute and chronic HCV infections.[17] After the initial diagnosis is made with serology, it usually is confirmed by assays that detect the virus's genomic RNA in the patient's serum or plasma.

The patient's HCV genotype should be identified so that the best treatment options can be determined. HCV genotyping can be accomplished using reverse transcription quantitative polymerase chain reaction (RT-qPCR) amplification. Three different RT-qPCR assessments usually are performed using different primers and probes specific to different genotypes of HCV. While direct sequencing of the HCV genome also can be performed, this method is usually not used clinically due to its technical complexity.[16]

TABLE 2 **Effect of mode of delivery on perinatal transmission rates of HCV in total study populations**

Author, year	Type of study; quality of evidence	No. of patients delivered by cesarean	No. of patients delivered vaginally	Perinatal transmission rate (%) in all patients delivered by cesarean	Perinatal transmission rate (%) in patients who had vaginal delivery	*P* value
Conte, 2000[22]	Prospective cohort; good	106	259	0.94	2.7	.297[a]
Okamoto, 2000[20,b]	Prospective cohort; poor	28	50	0.0	14	.045
European Paediatric Hepatitis C Virus Network, 2001[23]	Retrospective cohort; good	382	1018	7.3	9.9	.135[a]
Tajiri, 2001[24]	Prospective cohort; fair	24	90	4.2	8.8	.396
Ferrero, 2003[25]	Prospective cohort; fair	49	139	4.08	2.16	.472[a]
Mast, 2005[14,c]	Prospective cohort; good	30	151	3.3	4.0	.55
Marine-Barjoan, 2007[26]	Cohort; good	80	134	6.25	5.2	.752[a]
Murakami, 2012[21,b,d]	Prospective cohort; fair	31	75	0.0	13	.032
Delotte, 2014[27]	Prospective cohort; good	80	134	6.3	5.2	.752[a]
Garcia-Tejedor, 2015[28]	Retrospective cohort; fair	306	405	1.63	2.96	.25
Jhaveri, 2015[29]	Prospective cohort; poor	26	23	19.23	8.7	.42

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] *P* value not reported in original study.
[b] Overlapping populations.
[c] Study only reported data on mode of delivery for HIV-negative mothers.
[d] Study only reported cesarean deliveries that occurred before initial contractions or rupture of the membranes.

Modern treatments are effective

Introduced in 2011, direct-acting antiviral therapies are now the recommended treatment for HCV infection. These drugs inhibit the virus's replication by targeting different proteins involved in the HCV replication cycle. They are remarkably successful and have achieved sustained virologic response (SVR) rates greater than 90%.[11] The World Health Organization recommends several pangenotypic (that is, agents that work against all genotypes) direct-acting antiviral regimens for the treatment of chronic HCV infection in adults without cirrhosis (**TABLE 1**).[18,19]

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TABLE 3 Effect of mode of delivery on perinatal transmission rates of HCV in mothers co-infected with HIV

Author, year	Type of study; quality of evidence	No. of patients delivered by cesarean	No. of patients delivered vaginally	Perinatal transmission rate (%) in all patients delivered by cesarean	Perinatal transmission rate (%) in patients who had vaginal delivery	*P* value
European Paediatric Hepatitis C Virus Network, 2001[23]	Retrospective cohort; good	159	329	8.2	17.3	.008
Delotte, 2014[27]	Cohort; good	38	17	10.5	11.8	.892[a]

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] *P* value not reported in original study.

TABLE 4 Effect of mode of delivery on perinatal transmission rates of HCV in HIV-negative mothers

Author, year	Type of study; quality of evidence	No. of patients delivered by cesarean	No. of patients delivered vaginally	Perinatal transmission rate (%) in all patients delivered by cesarean	Perinatal transmission rate (%) in patients who had vaginal delivery	*P* value
European Paediatric Hepatitis C Virus Network, 2001[23]	Retrospective cohort; good	218	666	6.9	5.9	.58
Mast, 2005[14]	Cohort; good	30	151	3.3	4.0	.55

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Unfortunately, experience with these drugs in pregnant women is lacking. Many direct-acting antiviral agents have not been tested systematically in pregnant women, and, accordingly, most information about their effects in pregnant women comes from animal models.[11]

Perinatal transmission rates and effect of mode of delivery

We compiled data from 11 studies that reported the perinatal transmission rate of HCV associated with various modes of delivery. These studies were selected from a MEDLINE literature review from 1999 to 2019. The studies were screened by title and then by abstract. Inclusion was restricted to randomized controlled trials, cohort studies, and case-control studies written in English. Study quality was assessed as good, fair, or poor based on the study design, sample size, and analyses performed. The results from the total population of each study are reported in **TABLE 2** (page 41).[14,20-29]

Three studies separated data based on the mother's HIV status. The perinatal transmission rates of HCV for mothers co-infected with HIV are reported in **TABLE 3**.[23,27] The results for HIV-negative mothers are reported in **TABLE 4**.[14,23]

Finally, 2 studies grouped mothers according to their HCV viral load. All of the

TABLE 5 Effect of mode of delivery on perinatal transmission rates of HCV in mothers who had detectable HCV RNA

Author, year	Type of study; quality of evidence	No. of patients delivered by cesarean	No. of patients delivered vaginally	Perinatal transmission rate (%) in all patients delivered by cesarean	Perinatal transmission rate (%) in patients who had vaginal delivery	*P* value
Okamoto, 2000[20,a]	Prospective cohort; poor	18	41	0.0	17.1	.089
Murakami, 2012[21,a, b]	Prospective cohort; fair	20	56	0.0	17.9	.055

Abbreviation: HCV, hepatitis C virus.

[a] Overlapping populations.
[b] Study only reported cesareans that occurred before initial contractions or rupture of the membranes.

TABLE 6 Effect of mode of delivery on perinatal transmission rates of HCV in mothers with high viral loads, defined as ≥ 2.5 x 10^6 Eq/mL in the study by Okamoto, which is equivalent to ≥ 6.0 x 10^5 IU/mL in the study by Murakami

Author, year	Type of study; quality of evidence	No. of patients delivered by cesarean	No. of patients delivered vaginally	Perinatal transmission rate (%) in all patients delivered by cesarean	Perinatal transmission rate (%) in patients who had vaginal delivery	*P* value
Okamoto, 2000[20,a]	Cohort; poor	10	16	0.0	43.8	.023
Murakami, 2012[21,a, b]	Cohort; fair	9	22	0	40.9	.032

Abbreviation: HCV, hepatitis C virus.

[a] Overlapping populations.
[b] Study only reported cesareans that occurred before initial contractions or rupture of the membranes.

mothers in these studies were anti-HCV antibody positive, and the perinatal transmission rates for the total study populations were reported previously in TABLE 2. The results for mothers who had detectable HCV RNA are reported in **TABLE 5**.[20,21] High viral load was defined as ≥ 2.5 x 10^6 Eq/mL in the study by Okamoto and colleagues, which is equivalent to ≥ 6.0 x 10^5 IU/mL in the study by Murakami and colleagues due to the different assays that were used.[20,21] The perinatal transmission rates for mothers with a high viral load are presented in **TABLE 6**.[20,21]

For most, CD does not reduce HCV transmission

Nine of the 11 studies found that the mode of delivery did not have a statistically significant impact on the vertical transmission rate of HCV in the total study populations.[14,22-29] The remaining 2 studies found that the perinatal transmission rate of HCV was lower with cesarean delivery (CD) than with vaginal delivery.[20,21] When considered together, the results of these 11 studies indicate that CD does not provide a significant reduction in the HCV transmission rate in the general population.

Our review confirms the findings of others, including a systematic review by the US Preventive Services Task Force.[30] That investigation also failed to demonstrate any measurable increase in risk of HCV transmission as a result of breastfeeding.

Cesarean delivery may benefit 2 groups. Careful assessment of these studies, however, suggests that 2 select groups of patients with

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HCV may benefit from CD:

- mothers co-infected with HIV, and
- mothers with high viral loads of HCV.

In both of these populations, the vertical transmission rate of HCV was significantly reduced with CD compared with vaginal delivery. Therefore, CD should be strongly considered in mothers with HCV who are co-infected with HIV and/or in mothers who have a high viral load of HCV.

CASE Our recommendation for mode of delivery

The patient in our case scenario has both HIV infection and a very high HCV viral load. We would therefore recommend a planned CD at 38 to 39 weeks' gestation, prior to the onset of labor or membrane rupture. Although HCV infection is not a contraindication to breastfeeding, the mother's HIV infection is a distinct contraindication. ●

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Does BSO status affect health outcomes for women taking estrogen for menopause?

What do results from the Women's Health Initiative's 18-year follow-up study reveal?

Q&A with JoAnn E. Manson, MD, DrPH, NCMP

Do health effects of menopausal estrogen therapy differ between women with bilateral oophorectomy versus those with conserved ovaries? To answer this question a group of investigators performed a subanalysis of the Women's Health Initiative (WHI) Estrogen-Alone Trial,[1] which included 40 clinical centers across the United States. They examined estrogen therapy outcomes by bilateral salpingo-oophorectomy (BSO) status, with additional stratification by 10-year age groups in 9,939 women aged 50 to 79 years with prior hysterectomy and known oophorectomy status. In the WHI trial, women were randomly assigned to conjugated equine estrogens (CEE) 0.625 mg/d or placebo for a median of 7.2 years. Investigators assessed the incidence of coronary heart disease and invasive breast cancer (the trial's 2 primary end points), all-cause mortality, and a "global index"—these end points plus stroke, pulmonary embolism, colorectal cancer, and hip fracture—during the intervention phase and 18-year cumulative follow-up.

OBG MANAGEMENT caught up with lead author JoAnn E. Manson, MD, DrPH, NCMP, to discuss the study's results.

Dr. Manson is Professor of Medicine and the Michael and Lee Bell Professor of Women's Health at Harvard Medical School, Professor at the Harvard T. H. Chan School of Public Health, and Chief of the Division of Preventive Medicine at Brigham and Women's Hospital, Boston, Massachusetts. She is a past President of the North American Menopause Society.

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OBG MANAGEMENT: How many women undergo BSO with their hysterectomy?

JoAnn E. Manson, MD, DrPH, NCMP: Of the 425,000 women who undergo hysterectomy in the United States for benign reasons each year,[2,3] about 40% of them undergo BSO—so between 150,000 and 200,000 women per year undergo BSO with their hysterectomy.[4,5]

OBG MANAGEMENT: Although BSO is performed with hysterectomy to minimize patients' future ovarian cancer risk, does BSO have health risks of its own, and how has estrogen been shown to affect these risks?

Dr. Manson: First, yes, BSO has been associated with health risks, especially when it is performed at a young age, such as before age 45. It has been linked to an increased risk of heart disease, osteoporosis, cognitive decline, and all-cause mortality. According to observational studies, estrogen therapy appears to offset many of these risks, particularly those related to heart disease and osteoporosis (the evidence is less clear on cognitive deficits).[5]

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OBG MANAGEMENT: What did you find in your trial when you randomly assigned women in the age groups of 50 to 79 who underwent hysterectomy with and without BSO to estrogen therapy or placebo?

Dr. Manson: The WHI is the first study to be conducted in a randomized trial setting to analyze the health risks and benefits of estrogen therapy according to whether or not women had their ovaries removed. What we found was that the woman's age had a strong influence on the effects of estrogen therapy among women who had BSO but only a negligible effect among women who had conserved ovaries. Overall, across the full age range, the effects of estrogen therapy did not differ substantially between women who had a BSO and those who had their ovaries conserved.

However, there were major differences by age group among the women who had BSO. A significant 32% reduction in all-cause mortality emerged during the 18-year follow-up period among the younger women (below age 60) who had BSO when they received estrogen therapy as compared with placebo. By contrast, the women who had conserved ovaries did not have this significant reduction in all-cause mortality, or in most of the other outcomes on estrogen compared with placebo. Overall, the effects of estrogen therapy tended to be relatively neutral in the women with conserved ovaries.

Now, the reduction in all-cause mortality with estrogen therapy was particularly pronounced among women who had BSO before age 45. They had a 40% statistically significant reduction in all-cause mortality with estrogen therapy compared with placebo. Also, among the women with BSO, there was a strong association between the timing of estrogen initiation and the magnitude of reduction in mortality. Women who started the estrogen therapy within 10 years of having the BSO had a 34% significant reduction in all-cause mortality, and those who started estrogen more than 20 years after having their ovaries removed had no reduction in mortality.

FAST TRACK

The reduction in all-cause mortality with estrogen therapy was particularly pronounced among women who had BSO before age 45. They had a 40% statistically significant reduction in all-cause mortality with estrogen therapy compared with placebo.

OBG MANAGEMENT: Do your data give support to the timing hypothesis?

Dr. Manson: Yes, our findings do support a timing hypothesis that was particularly pronounced for women who underwent BSO. It was the women who had early surgical menopause (before age 45) and those who started the estrogen therapy within 10 years of having their ovaries removed who had the greatest reduction in all-cause mortality and the most favorable benefit-risk profile from hormone therapy. So, the results do lend support to the timing hypothesis.

By contrast, women who had BSO at hysterectomy and began hormone therapy at age 70 or older had net adverse effects from hormone therapy. They posted a 40% increase in the global index—which is a summary measure of adverse effects on cardiovascular disease, cancer, and other major health outcomes. So, the women with BSO who were randomized in the trial at age 70 and older had unfavorable results from estrogen therapy and an increase in the global index, in contrast to the women who were below age 60 or within 10 years of menopause.

OBG MANAGEMENT: Given your study findings, in which women would you recommend estrogen therapy? And are there groups of women in which you would advise avoiding estrogen therapy?

Dr. Manson: Current guidelines[6,7] recommend estrogen therapy for women who have early menopause, particularly an early surgical menopause and BSO prior to the average age at natural menopause. Unless the woman has contraindications to estrogen therapy, the recommendations are to treat with estrogen until the average age of menopause—until about age 50 to 51.

Our study findings provide reassurance that, if a woman continues to have indications for estrogen (vasomotor symptoms, or other indications for estrogen therapy), there is relative safety of continuing estrogen-alone therapy through her 50s, until age 60. For example, a woman who, after the average age of menopause continues to have vasomotor

symptoms, or if she has bone health problems, our study would suggest that estrogen therapy would continue to have a favorable benefit-risk profile until at least the age of 60. Decisions would have to be individualized, especially after age 60, with shared decision-making particularly important for those decisions. (Some women, depending on their risk profile, may continue to be candidates for estrogen therapy past age 60.)

So, this study provides reassurance regarding use of estrogen therapy for women in their 50s if they have had BSO. Actually, the women who had conserved ovaries also had relative safety with estrogen therapy until age 60. They just didn't show the significant benefits for all-cause mortality. Overall, their pattern of health-related benefits and risks was neutral. Thus, if vasomotor symptom management, quality of life benefits, or bone health effects are sought, taking hormone therapy is a quite reasonable choice for these women.

By contrast, women who have had a BSO and are age 70 or older should really avoid initiating estrogen therapy because it would follow a prolonged period of estrogen deficiency, or very low estrogen levels, and these women appeared to have a net adverse effect from initiating hormone therapy (with increases in the global index found).

OBG MANAGEMENT: Did taking estrogen therapy prior to trial enrollment make a difference when it came to study outcomes?

Dr. Manson: We found minimal if any effect in our analyses. In fact, even the women who did not have prior (pre-randomization) use of estrogen therapy tended to do well on estrogen-alone therapy if they were younger than age 60. This was particularly true for the women who had BSO. Even if they had not used estrogen previously, and they were many years past the BSO, they still did well on estrogen therapy if they were below age 60. ●

FAST TRACK

This study provides reassurance regarding use of estrogen therapy for women in their 50s if they have had BSO. And, the women who had conserved ovaries also had relative safety with estrogen therapy until age 60.

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Should secondary cytoreduction be performed for platinum-sensitive recurrent ovarian cancer?

Such practice should be questioned, according to authors of a phase 3 randomized, controlled trial. In the study, 485 patients with platinum-sensitive recurrent resectable disease who had received 1 previous therapy and had a 6-month or more platinum-free interval (an interval during which no platinum-based chemotherapy was used) were randomly assigned to receive platinum-based chemotherapy or to undergo surgical cytoreduction followed by platinum-based chemotherapy. There were no statistical differences in overall survival, with a trend favoring nonsurgical patients, or progression-free survival, with a trend favoring surgical patients. However, we would recommend using caution in applying the study data to patients with different platinum-free intervals or low-volume disease limited to the pelvis.

FAST TRACK

This is the first RCT to explore the management option of secondary cytoreduction in women with recurrent ovarian cancer

Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med. 2019;381:1929-1939.

EXPERT COMMENTARY

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Ovarian cancer represents the most lethal gynecologic cancer, with an estimated 14,000 deaths in 2019.[1] While the incidence of this disease is low in comparison to uterine cancer, the advanced stage at diagnosis portends poor prognosis. While stage is an independent risk factor for death, it is also a risk for recurrence, with more than 80% of women developing recurrent disease.[2-4] Secondary cytoreduction remains an option for patients in which disease recurs; up until now this management option was driven by retrospective data.[5]

Details of the study

Coleman and colleagues conducted the Gynecologic Oncology Group (GOG) 0213 trial—a

phase 3, multicenter, randomized clinical trial that included 485 women with recurrent ovarian cancer. The surgical objective of the trial was to determine whether secondary cytoreduction in operable, platinum-sensitive (PS) patients improved overall survival (OS).

Patients were eligible to participate in the surgical portion of the trial if they had PS measurable disease and had the intention to achieve complete gross resection. Women with ascites, evidence of extraabdominal disease, and "diffuse carcinomatosis" were excluded. The primary and secondary end points were OS and progression-free survival (PFS), respectively.

Results. There were no statistical differences between the surgery and no surgery groups with regard to median OS (50.6 months vs 64.7 months, respectively; hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.97–1.72) or median PFS (18.9 months vs 16.2 months; HR, 0.82; 95% CI, 0.66 to 1.01). When comparing patients in which complete gross resection was achieved (150 patients vs 245 who did not receive surgery), there was only a statistical difference in PFS in favor of the surgical group (22.4 months vs 16.2 months; HR, 0.62; 95% CI, 0.48–0.80).

Of note, 67% of the patients who received surgery (63% intention-to-treat) were debulked to complete gross resection. There were 33% more patients with extraabdominal disease (10% vs 7% of total patients in each group) and 15% more patients with upper abdominal disease (40% vs 33% of total patients in each group) included in the surgical group. Finally, the median time to chemotherapy was 40 days in the surgery group versus 7 days in the no surgery group.

Study strengths and weaknesses

The authors deserve to be commended for this well-designed and laborious trial, which is the first of its kind. The strength of the study is its randomized design producing level I data.

Study weaknesses include lack of reporting of *BRCA* status and the impact of receiving targeted therapies after the trial was over. It is well established that *BRCA*-mutated patients have an independent survival advantage, even when taking into account platinum sensitivity.[6-8] *BRCA* status of the study population is not specifically addressed in this paper. The authors noted in the first GOG 0213 trial publication, which assessed bevacizumab in the recurrent setting, that *BRCA* status has an impact on patient outcomes. Subsequently, they state that they do not report *BRCA* status because "…its independent effect on response to an anti-angiogenesis agent was unknown," but it clearly would affect survival analysis if unbalanced between groups.[9]

Similarly, in the introduction to their study, Coleman and colleagues list availability of maintenance therapy, for instance poly ADP (adenosine diphosphate–ribose) polymerase (PARP) inhibitors, as rationale for conducting their trial. They subsequently cite this as a possible reason that the median overall survival was 3 times longer than expected. However, they provide no data on which patients received maintenance therapy, which again could have drastically affected survival outcomes.[10] They do report in the supplementary information that, when stratifying those receiving bevacizumab adjuvantly during the trial, the median OS was comparable between the surgical and nonsurgical groups (58.5 months vs 61.7 months).

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

This is the first randomized clinical trial conducted to assess whether secondary surgical cytoreduction is beneficial in PS recurrent ovarian cancer patients. It provides compelling evidence to critically evaluate whether surgical cytoreduction is appropriate in a similar patient population. However, we would recommend using caution applying these data to patients who have different platinum-free intervals or low-volume disease limited to the pelvis.

The trial is not without flaws, as the authors point out in their discussion, but currently, it is the best evidence afforded to gynecologic oncologists. There are multiple trials currently ongoing, including DESTOP-III, which had similar PFS results as GOG 0213. If consensus is reached with these 2 trials, we believe that secondary cytoreduction will be utilized far less often in patients with recurrent ovarian cancer and a long platinum-free interval, thereby changing the current treatment paradigm for these patients.

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The authors discuss the presence of patient selection bias as a weakness in the study. Selection bias is evident in this trial (as in many surgical trials) because patients with a limited volume of disease were selected to participate over those with large-volume disease. It is reasonable to conclude that this study is likely selecting patients with less aggressive tumor biology, not only evident by low-volume disease at recurrence but also by the 20.4-month median platinum-free interval in the surgical group, which certainly affects the trial's validity. Despite being considered PS, the disease biology in a patient with a platinum-free interval of 20.4 months is surely different from the disease biology in a patient with a 6.4-month platinum-free interval; therefore, it is difficult to generalize these data to all PS recurrent ovarian cancer patients. Similarly, other research has suggested strict selection criteria, which was not apparent in this study's methodology.[11] While the number of metastatic sites were relatively equal between the surgery and no surgery groups, there were more patients in the surgical group with extraabdominal disease, which the authors used as an exclusion criterion.

Lastly, the time to treatment commencement in each arm, which was 40 days for the surgical arm and 7 days in the nonsurgical arm, could represent a flaw in this trial. While we expect a difference in duration to account for recovery time, many centers start chemotherapy as soon as 21 days after surgery, which is almost half of the median interval in the surgical group in this trial. While the authors address this by stating that they completed a landmark analysis, no data or information about what time points they used for the analysis are provided. They simply report an interquartile range of 28 to 51 days. It is hard to know what effect this may have had on the outcome. ●

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PRODUCT Update

NEW SACRAL NEUROMODULATION DEVICE

Axonics Modulation Technologies, Inc. announced the first implantation of its recently US Food and Drug Administration (FDA)-cleared, implantable, rechargeable sacral neuromodulation device. The implantation was the first to occur outside of a clinical study setting. The device is designed to reduce urinary and bowel dysfunction symptoms and reestablish pelvic floor function by restoring communication between the bladder and bowel to the brain. The **Axonics r-SNM System** is the first sacral neuromodulation device to be sold in the world. It is a miniaturized neurostimulator approximately the size of a USB stick and is qualified to operate for at least 15 years. The device can be safely left in place during full-body magnetic resonance imaging, says **Axonics**.

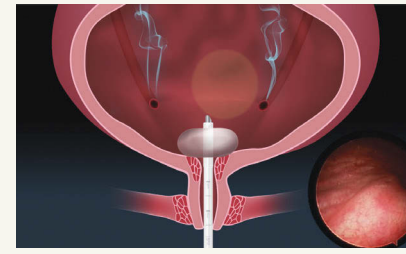
FOR MORE INFORMATION, VISIT: https://www.axonics.com/

CERVICAL SEAL FOR HYSTEROSCOPIC DEVICES

Hologic has expanded its hysteroscopy portfolio with the launch of its **Omni™ Lok cervical seal**. The seal is designed to help maintain uterine distention and improve procedural efficiency in the operating room (OR) by minimizing fluid leakage during hysteroscopic procedures. **Hologic** says that **Omni Lok** is compatible with the MyoSure® and Omni™ hysteroscopes and reduces fluid leakage by an average of 94%. The **Omni Lok cervical seal** is commercially available in the United States and Canada. The device should not be used in a patient with a contraindication to hysteroscopy, says **Hologic**.

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

UNIVERSAL CYSTOSCOPY SIMPLIFIED



Emmy Medical announces the **CystoSure® XL**, an all-in-one silicone urinary catheter with an additional port for the introduction of a conventional hysteroscope to conduct simple cystoscopy. An addition to the CystoSure Silicone Cystoscopy Catheters, the new **CystoSure XL** provides a solution for the surgeon to view the bladder in every patient every time without the need to open and introduce a complete cystoscopy tray and instrumentation, says **Emmy**. According to the manufacturer, the CystoSure System combines the familiarity of a urinary catheter with the functionality of a cystoscope into a singular product providing easy viewing access of the bladder at any time in an OR or office procedure.

FOR MORE INFORMATION, VISIT: https://cystosure.com/

NEXT FRONTIER IN VACCINE IMMUNIZATION

Pfizer announces that it is embarking on the next frontier in vaccine immunization by conducting several studies of infant protection through maternal vaccination. While no vaccine currently is licensed for use in pregnant women to protect her infant, multiple studies have demonstrated that this can be done, says **Pfizer**. The company is currently investigating, in phase 1 and 2 studies, vaccines for Group B Streptococcus (GBS) and respiratory syncytial virus (RSV).

Globally, there are 410,000 cases of GBS every year. GBS is most common in newborns; women who are carriers of the GBS bacteria may pass it on to their newborns during labor and birth. An estimated 10% to 30% of pregnant women carry the GBS bacteria. The disease can manifest as sepsis, pneumonia, and meningitis, with potentially fatal outcomes for some. A maternal vaccine may prevent 231,000 infant and maternal GBS cases, says **Pfizer**.

According to **Pfizer**, RSV causes more hospitalizations each year than influenza among young children, with an estimated 33 million cases globally each year in children less than age 5 years.

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

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