Perinatal Vaccination
A practical guide for increasing vaccine uptake

Ilona Telefus Goldfarb, MD, MPH, and Laura E. Riley, MD

ContemporaryOBGYN.net
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.
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:

BREVIEW 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 use 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 non-radiopaque etonogestrel implant is inserted subcutaneously 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 veins 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 be used in women who have

• Known or suspected pregnancy
• Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, new 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, and experience with combination (estrogen plus progestin) oral contraceptives.

Complications of Insertion and Removal

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

If NEXPLANON is inserted deeply (intramuscular or in the fascial, neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subcutaneously just under the skin at the inner side of the non-dominant upper arm over 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 intravascular procedures may be needed for removal.

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

Experiential surgery without knowledge of the exact location of the implant is strongly discouraged. Recognition of the implant 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 located in the chest. Healthcare providers should be reminded with the anatomy should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or recurrence of a pre-existing 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 (abnormal, 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 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%). Irregular bleeding (10.6%) was the single most frequent reason for stopped treatment, while amenorrhea (0.3%) was cited less frequently.

Bleeding Patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of patients bleeds on 15 day or 21 day cycles are summarized in Table 1.

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

<table>
<thead>
<tr>
<th>Days of Sporadic or Bleeding</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Days</td>
<td>24%</td>
</tr>
<tr>
<td>1-7 Days</td>
<td>13%</td>
</tr>
<tr>
<td>8-21 Days</td>
<td>30%</td>
</tr>
<tr>
<td>≥21 Days</td>
<td>33%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infraguent</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)</td>
<td>33.6</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
<td>22.2</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
<td>17.7</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
<td>6.7</td>
</tr>
</tbody>
</table>

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

Side Effects:

• 0 Days: Amenorrhea
• 1-7 Days: Spotting or Bleeding
• 8-21 Days: Heavy Bleeding
• ≥21 Days: Frequent Bleeding

Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Carefully monitor prediabetic and diabetic women using NEXPLANON.

Carbohydrate and Lipid Metabolic Effects

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 among users of combination hormonal contraceptives. 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 the 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, photopsia, 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 in 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods of contraception.

The progestin-etonogestrel pharmacokinetics may be 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 3.6 pounds after one year and 5.1 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 of contraception.

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 by a week or two after removal of the implant, and ovulatory menstrual periods 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.
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 Lens
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Silk/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. Thyrroxine 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-radioopaque etonogestrel implant (NEXPLANON® [etonogestrel implant]) (11.1% of women). Adverse reactions that resulted in a rate of discontinuation >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-Radioopaque Etonogestrel Implant (NEXPLANON)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding irregularities†</td>
<td>11.1%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>2.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.5%</td>
</tr>
<tr>
<td>Acne</td>
<td>1.3%</td>
</tr>
<tr>
<td>Depression‡</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

† 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.

Other adverse reactions that were reported by at least 5% of subjects in the non-radioopaque 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-Radioopaque Etonogestrel Implant (NEXPLANON)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9%</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>14.5%</td>
</tr>
<tr>
<td>Weight increase</td>
<td>13.7%</td>
</tr>
<tr>
<td>Acne</td>
<td>13.5%</td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.8%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.5%</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>9.6%</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.2%</td>
</tr>
<tr>
<td>Dysemenorrhea</td>
<td>7.2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.8%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>6.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Pain</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6%</td>
</tr>
<tr>
<td>Depression</td>
<td>5.5%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>5.4%</td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

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, hematomas (0.3%), bruising (2.5%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives
Substances increasing the plasma concentrations of HCIs: Co-administration of certain HCIs and other appropriate moderate CYP3A4 inhibitors such as voriconazole, verapamil, fexofenadine, ketocazole, grapefruit juice, or ketoconazole may increase the serum concentrations of progesterone, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors may increase the plasma concentrations of progesterone. If co-administration may be necessary, the concentration of the other drug may need to be significantly increased.

Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>90 days (excluding amenorrhea)</th>
<th>N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td>24.9%</td>
</tr>
<tr>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
<td>6.7%</td>
</tr>
<tr>
<td>Discontinued</td>
<td>11.1%</td>
</tr>
<tr>
<td>Interval 1</td>
<td>42%</td>
</tr>
<tr>
<td>Interval 2</td>
<td>42%</td>
</tr>
<tr>
<td>Interval 3</td>
<td>16%</td>
</tr>
</tbody>
</table>

Pharmacodynamics
The systemic exposure of the implant is relatively constant for at least 2 years. The mean serum concentration of etonogestrel in patients who have received NEXPLANON for up to 24 months was 1.4 ± 0.7 ng/mL. This can be compared to the mean steady state serum concentration in women who received an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.05 mg levonorgestrel once daily of 1.3 ± 0.6 ng/mL.

Pharmacokinetics
The etonogestrel implant is released into the subdermal tissue beneath the skin, where it is metabolized into 3 metabolites. One of these metabolites is 16a-hydroxy-19-nortestosterone. The remaining 2 metabolites are both glucuronides of the same molecule which are not biologically active.

In patients, etonogestrel concentrations were 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. OVERDOSE

Overdose 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 per implant, no evidence of increased incidence of tumors or tumor multiplicity was found. There were no differences in the incidence of tumors in female rats or male rats treated with the etonogestrel implant when compared to control animals. Additionally, no teratogenic effects were observed when NEXPLANON was administered to pregnant rats.

Some studies suggest that the use of 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 activity between women who use hormonal contraceptives and those who do not. 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].

OBGYN0220_CV1-003_nexplanon.indd 3
24/2/20 8:19 AM

For more detailed information, please read the Prescribing Information.

US-XP1-00588 05/19

USPI-MK8415-IPTX-1810r020

Copyright © 2019 Merck Sharp & Dohme B.V., a subsidiary of Merck & Co., Inc. All rights reserved.

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.

USP-INX-00041518

Revised 06/2018
CHAIRMAN’S LETTER

Limiting harm

Thanks in large part to the Internet, we now have at our fingertips more information than ever before. However, not all of it is factual. Therefore, as healthcare providers who have taken the Hippocratic oath, OB/GYNs have an obligation to limit the harm of misinformation by educating themselves and their patients. This is the focus of much of our February issue.

In this month’s cover story, Ilona Telefus Goldfarb, MD, MPH, and Laura E. Riley, MD, discuss the importance of perinatal vaccination and which vaccines are recommended. The authors also touch briefly on how to respond to vaccine myths. If you have had success with a specific strategy for treating patients who felt strongly about vaccine effectiveness, please email bschwartz@mmhgroup.com.

In this year’s first installment of our Complex Contraceptives series, Charisse S. Loder, MD, MSC, and Lauren Owens, MD, MPH, provide tips for counseling hypertensive patients on their contraception options. The authors discuss the safety of various contraceptives, how hypertension impacts pregnancy, and provide a case scenario challenge.

Providers often face difficult clinical situations concerning the best hormonal regimen to choose in women at increased risk for venous thromboembolism (VTE). Emma Lawrence, MD, Elisabeth Quint, MD, and Angela Weyand, MD, review the current literature and guidelines to assist providers in evidence-based management of abnormal uterine bleeding with progestins so that you and your patients can be well-informed about their options and any associated risks.

As always, if you have any comments on any of the topics discussed, please be sure to contact us at COGEditorial@mmhgroup.com or bschwartz@mmhgroup.com. For even more content, visit us online at Contemporaryobgyn.net.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
IN THIS ISSUE

FEBRUARY 2020

VOLUME 65 | NUMBER 02

CONTEMPORARY OB/GYN
(Print ISSN#0090-3159, DIGITAL ISSN#2150-6264), is published monthly by MultiMedia Healthcare LLC, 230 W Superior ST, STE 400, Duluth MN 55802. One-year subscription rates: $110.00 per year (USA and Possessions); $140.00 per year (elsewhere). Single copies (prepaid only) $12.00 in the USA; $18.00 per copy elsewhere. Include $6.50 per order plus $2.00 for US postage and handling. Periodic postage paid at Duluth, MN 55806 and additional mailing offices: POSTMASTER: Please send address changes to Contemporary OB/GYN, PO Box 467, Crestview NJ 08519. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Printed in USA. Subscription inquiries/address changes: call toll-free 888-527-7008, or dial direct 218-740-6477.

THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/BreastCancerCME

CONTEMPORARY OB/GYN

GYNECOLOGY
10 Progestins for AUB in women at risk of VTE
EMMA LAWRENCE, MD, ELISABETH QUINT, MD, AND ANGELA WEYAND, MD
A review of current literature and guidelines plus four patient cases centered on commonly used progestins for AUB management.

LIFE TRANSITIONS
14 Menopausal symptoms through the seasons
Menopausal symptoms appear to exhibit seasonal variation, according to new research.

WELL WOMAN
16 Ovarian cancer and powder
A recent study shows no significant association between use of powder in the genital area and ovarian cancer.

VULVOVAGINAL DISEASE
17 Too many teen pelvic exams and Pap tests?
Many young women receive gynecologic exams that may be unnecessary and not in compliance with the latest ACOG guidance.

CONTRACEPTION
18 Tips for counseling hypertensive patients
CHARISSE M. LODER, MD, MSC, AND LAUREN OWENS, MD, MPH
This installment from our Complex Contraceptives series examines treatments and contraception considerations for patients with high blood pressure.

OBSTETRICS
06 Perinatal vaccinations
ILONA TELEFUS GOLDFARB, MD, MPH, AND LAURA E. RILEY, MD
An evidence-based summary of the vaccines recommended for the various stages of pregnancy.

IN ADDITION
28 Legally Speaking
ANDREW I. KAPLAN, ESQ.
This case features multiple defendants and illustrates why coordinating a unified defense should be the primary objective in these types of trials.

THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/BreastCancerCME

CONTEMPORARY OB/GYN

CONTEMPORARY OB/GYN does not verify any claims or other information appearing in any of the advertisements contained in the publication, and cannot take responsibility for any losses or other damages incurred by readers in reliance of such content.

To subscribe, call toll-free 888-527-7008. Outside the U.S. call 218-740-6477.
Perinatal vaccination
a practical guide for obstetric providers

When clinicians are knowledgeable about the benefits of vaccinations, vaccination rates among patients increase.

by ILONA TELEFUS GOLDFARB, MD, MPH, AND LAURA E. RILEY, MD

Protecting pregnant women and their newborns by offering timely and effective vaccinations is a critical component of disease prevention, particularly given the rise of vaccine-preventable disease in the United States and around the globe. Studies show that when clinicians are knowledgeable about the benefits of vaccines and offer them to their patients, uptake of vaccination rises. This is particularly true during pregnancy, when patients are concerned about vaccine safety and efficacy.

In this review, we provide an evidence-based summary of the vaccines that are recommended for women preconception, during pregnancy, and postpartum and provide counseling tips to help providers achieve the highest vaccine uptake rates possible.

### Acceptable evidence of immunity against measles

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Acceptable evidence of immunity against measles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptable presumptive evidence of immunity against measles includes at least one of the following:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Written documentation of adequate vaccination (one or two doses):</strong></td>
<td></td>
</tr>
<tr>
<td>• Documentation of two prior MMR vaccine doses are required for “high-risk” individuals.</td>
<td></td>
</tr>
<tr>
<td>- <strong>HIGH-RISK</strong> is defined as healthcare workers, international travelers, students in secondary educational institution (college/university).</td>
<td></td>
</tr>
<tr>
<td>• Documentation of one prior MMR vaccine dose is required for “low-risk” individuals.</td>
<td></td>
</tr>
<tr>
<td>- <strong>LOW-RISK</strong> is defined as anyone not meeting the above high-risk criteria including pregnant women.</td>
<td></td>
</tr>
<tr>
<td>• Healthcare providers should not accept verbal reports of vaccination without written documentation as presumptive evidence of immunity.</td>
<td></td>
</tr>
<tr>
<td>• In areas of ongoing outbreaks where there is sustained transmission in close-knit communities, serologic testing for measles IgG at the initiation of prenatal care can be considered in women without documented immunity to measles.</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory evidence of immunity (Measles IgG)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory confirmation of measles infection (Measles PCR)</strong></td>
<td></td>
</tr>
</tbody>
</table>

---

**DR. GOLDFARB** is a maternal-fetal medicine doctor at Harvard Medical School, Massachusetts General Hospital, Boston, MA.

**DR. RILEY** is a maternal fetal medicine doctor and Chair of the Department of Obstetrics and Gynecology at Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY.
Preconception

The preconception period offers a unique opportunity to optimize a woman’s health for pregnancy and beyond.

**INFLUENZA**

Influenza infection during pregnancy has been associated with severe maternal illness, pregnancy loss, and preterm birth. Immunity confers significant benefits to both pregnant women and their offspring. Generally available for administration from late August through March of each year to correspond with the influenza season (timing may vary by region), the trivalent or quadrivalent, inactivated influenza vaccine should be given to all individuals older than age 6 months, including women considering pregnancy. Do not administer live vaccine (LAIV, Flumist) to women who may be pregnant but there is no contraindication to their family members receiving the live vaccine.

**MEASLES, MUMPS, AND RUBELLA (MMR)**

Given the global measles outbreak, the Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG) recommend assessing measles immunity in addition to rubella immunity. The CDC recommends an evaluation of either a patient’s vaccine record or confirmatory measles serology to prove immunity (Table 1). While a single prior MMR dose may be adequate for some women, patients at high risk for exposure to measles should demonstrate proof of two doses. Many providers ask if the demonstration of rubella immunity from a prior pregnancy is adequate to confirm measles immunity. While rubella immunity is generally correlated with receipt of at least one MMR vaccine, that is not a valid surrogate for measles immunity. If the appropriate number of MMR doses has not been documented or the vaccine record is not available, measles serology can be obtained, and an MMR vaccine booster administered to patients with a negative Measles IgG antibody result. After receiving the MMR vaccine—a live, attenuated vaccine—women should wait 4 weeks prior to attempting pregnancy, given theoretical risks to the fetus with live vaccines. However, if pregnancy occurs inadvertently within the 4-week window, patients should be reassured that there have been no reports of fetal harm due to this exposure.

Assessing rubella immunity has been a longstanding part of prenatal testing given the preventability of congenital rubella syndrome for those who have been adequately vaccinated with MMR. Therefore, women who are either measles non-immune or rubella non-immune should receive a MMR vaccine.

### TABLE 2

<table>
<thead>
<tr>
<th>Risk-based vaccination for HAV, HBV, and pneumococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B risk factors</strong>¹⁴</td>
</tr>
<tr>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Current or former injection drug users</td>
</tr>
<tr>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Travel to area of high prevalence for &gt; 6 months</td>
</tr>
<tr>
<td>Healthcare personnel</td>
</tr>
<tr>
<td>Dialysis/ESRD patients</td>
</tr>
<tr>
<td>Multiple sexual partners</td>
</tr>
<tr>
<td>Sexually transmitted infections</td>
</tr>
<tr>
<td>Household contact or sexual partner of person with chronic Hepatitis B</td>
</tr>
</tbody>
</table>

Abbreviations: ESRD, end-stage renal disease; HAB, hepatitis B virus; HAV, hepatitis A virus.
non-immune should be vaccinated in the preconception period.

**VARICELLA ZOSTER VIRUS (VZV)**
Given the significant risk of maternal and fetal harm with primary VZV infection during pregnancy, assessing a woman’s VZV immunity preconception will allow you to provide her with varicella vaccine if she is not immune. A history of chicken pox infection, evidence of VZV vaccination, or positive VZV serologies are all acceptable means to assess immunity. For a woman without proof of immunity, a preconception VZV vaccine can protect her from life-threatening pneumonia and her fetus from congenital varicella syndrome. Because the vaccine for VZV is live attenuated, vaccination should be performed, at least 4 weeks prior to attempted conception given the theoretical concern for causing birth defects.17

Other vaccines may be indicated, particularly in women who have medical illnesses that put them at high risk for vaccine-preventable illnesses. Obtaining a thorough preconception immunization history as part of routine care also may uncover adult women who have missed prior vaccination opportunities.

**HEPATITIS B (HPV) AND HEPATITIS A (HAV)**
HAB and HAV immunity is particularly important for women planning pregnancy who are at high risk for these infections (Table 2). HBV vaccine is administered in a three-dose series (0, 1, and 4 months apart). The vaccine for HAV is inactivated and can be given pre-exposure as a two-dose series (6 to 18 months apart), or as post-exposure prophylaxis. These vaccines are recombinant and have not been associated with adverse fetal outcomes. Therefore, no waiting period is required after administration in the preconception period and they can be administered during pregnancy if needed or if the three-dose series has not been completed.15

**PNEUMOCOCCUS**
The pneumococcal vaccine is indicated for adult women who are at high risk for serious complications from pneumococcus, such as individuals who smoke or who have asthma or diabetes. Additional indications are summarized in Table 2.14-17 There are two pneumococcal vaccines. For adults with risk factors, the CDC recommends administering one dose of PCV13 followed by the PPSV23 dose at least 8 weeks later without a delay in conception.16-18

**HUMAN PAPILLOMAVIRUS (HPV)**
Vaccination against HPV is recommended to prevent new HPV infections and HPV-associated diseases, including cervical cancer. While this vaccine remains targeted to young adolescents, the Advisory Committee on Immunization Practices (ACIP) now endorses catch-up HPV vaccination for all individuals through age 26 years. Adults who have previously been infected with one or more HPV types can still benefit from protection for other types available in the vaccine. For adults aged 27 through 45 years, and at risk for new HPV infection, decisions...
around vaccination should be made using a shared clinical decision-making model.\textsuperscript{19,20} HPV vaccination for patients older than age 15 should follow a three-dose regimen (0, 1 to 2 and 6 months). Counseling and guidance about the benefits of HPV vaccination are ideal for preconception women who plan for pregnancy in greater than 6 months. While the HPV vaccine is not recommended during pregnancy, inadvertent HPV vaccination during pregnancy is not associated with adverse events for a woman or her fetus.\textsuperscript{19}

**During pregnancy**

Incorporating vaccine administration as a routine part of prenatal care is key to protecting pregnant women and their offspring from vaccine-preventable diseases. Evidence-based strategies to build a robust vaccination program embedded within an obstetrical practice include: staff education for all individuals who encounter the patient (front desk, medical assistants, lab techs, nurses, midwives, and physicians), patient education in multiple languages, and standing-order sets.\textsuperscript{2,3,21} When vaccines are not available within your office or clinic, encouraging women to receive needed vaccines at the pharmacy or through their employer is also important, but a less effective strategy.

Vaccines that should be given to every pregnant woman during every pregnancy include influenza during flu season and Tdap.\textsuperscript{5,22,23} As noted previously, other vaccines may be given if women have high-risk comorbidities or are midway through a vaccine series, HAV, HAB, and the pneumococcal vaccine should be considered for administration during pregnancy based on a patient’s medical history and additional risk factors (Table 3). Obstetrical providers who are knowledgeable about vaccine safety and efficacy and prepared to debunk myths about vaccines in pregnancy will have the highest rates of vaccine uptake (Table 4).\textsuperscript{1,2}

**Postpartum**

Attention to vaccination continues as we care for women in the postpartum period. All women who are found to be rubella, measles, or VZV non-immune during pregnancy should receive these live-attenuated virus vaccines postpartum without concerns about lactation. Postpartum and lactating women who are age 26 or younger and who have not previously received HPV vaccination should have this series initiated. The vaccine may also be considered for women older than age 26 who are at risk for HPV exposure.\textsuperscript{19-23} Finally, postpartum and lactating women with risk factors (Table 2) who have not previously been vaccinated should receive HAV, HBV, and pneumococcal vaccines according to ACOG and CDC recommendations.\textsuperscript{23}

**TABLE 4**  **Responses to vaccine myths**

<table>
<thead>
<tr>
<th>Myth</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Flu shot makes me sick</td>
<td>An uncommon reaction from the flu vaccine is headache, muscle aches, and low-grade fever which can sometimes be confused with getting the flu, however, flu vaccines are made from a killed or very weakened virus, which is not infectious. In addition, it is useful to help patients distinguish cold symptoms from the flu.</td>
</tr>
<tr>
<td>Vaccines cause autism</td>
<td>Many studies have been conducted reviewing mercury (thimerosal), vaccines, and autism. No study has ever shown a positive relationship between vaccines, mercury, and subsequent autism diagnosis. The only vaccines that contain thimerosal are multidose-vial presentations of influenza vaccines.</td>
</tr>
<tr>
<td>I’m young and healthy, so I never get the flu shot</td>
<td>Pregnant women who get the flu suffer more severe symptoms than non-pregnant women. Even healthy pregnant women can become severely ill and even die from influenza infection.</td>
</tr>
<tr>
<td>Vaccines pose a risk to my unborn baby</td>
<td>Vaccines recommended in pregnancy have proven to be safe in all trimesters. Since 2004, the CDC and ACOG have recommended vaccinations such as influenza during any trimester.</td>
</tr>
<tr>
<td>Vaccines in the first trimester will cause miscarriage</td>
<td>Vaccines such as influenza have been given to millions of pregnant women over decades. No relationship has been shown between influenza vaccination and birth defects and miscarriage.</td>
</tr>
<tr>
<td>I can get my Tdap postpartum</td>
<td>Postpartum vaccination of women as a strategy to protect newborns from pertussis is not effective. Vaccination during pregnancy provides for passive immunity to infants, protecting them from pertussis until they are able to get their vaccination at 2 months.</td>
</tr>
</tbody>
</table>

FOR REFERENCES VISIT contemporaryobgyn.net/PerinatalVaccination
Abnormal uterine bleeding (AUB) is common among premenopausal women. For many women, hormonal medications including estrogen and/or progestins is the mainstay of AUB management. Every provider, no matter how experienced with hormonal management of AUB, faces difficult clinical situations concerning the best hormonal regimen to choose in women at increased risk for venous thromboembolism (VTE).

Incidence of VTE in women of childbearing age is 1 to 10 in 10,000 yearly. The risk increases with age, weight, smoking, certain clotting disorders, and use of combined hormonal contraceptives. Initially it was thought that estrogen alone increased VTE risk, however, it is now known that different progestins have varied VTE risk. This article reviews the current literature and guidelines to assist ob/gyns in evidence-based management of AUB with progestins, focusing on risk of VTE. Four patient cases are presented, each centered on a commonly used progestin for management of AUB in premenopausal women: the levonorgestrel intrauterine system (LNG-IUS), depot medroxyprogesterone, norethindrone acetate (DMPA), and megestrol acetate. Also included are guidance on patient counseling and a review of the available literature (Table 1).

Patient #1: LNG-IUS
A 25-year-old G0P0 with systemic lupus erythematosus (SLE) and positive anti-phospholipid antibodies presents to discuss management of heavy periods, a hemoglobin of 10.5 g/dL and a need for contraception. She denies a personal or family history of VTE. The woman doesn’t remember to take her other medications regularly and desires an option that lightens her cycle, while also providing longer-term effective contraception.

You counsel your patient that the Centers for Disease Control and Prevention Medical Eligibility Criteria (CDC-MEC) guidelines characterize the LNG-IUS as category 3 (risks generally outweigh benefits) in patients with SLE and positive antiphospholipid antibodies. However, you also educate her that citations behind the MEC recommendation are mostly based on a theoretical risk of VTE rather than studies of LNG-IUS use in her specific situation. Based on this patient’s positive antiphospholipid antibodies, the MEC guidelines recommend only one option for her: the copper IUD; how-
ever, with her heavy bleeding and mild anemia, it is not an ideal option. You counsel her that the literature does not demonstrate any increased risk of VTE with LNG-IUS use, in both low- and high-risk populations, and engage in shared decision-making.

LITERATURE
The LNG-IUS is available in several versions, with its active progestin component levonorgesterol ranging from 13.5 to 52 mg. With use of the device, the stable plasma level of levonorgestrel is at most approximately 3% of the level seen with a levonorgestrel-containing combination oral contraceptive (COC) pill. The 52-mg LNG-IUS is approved by the US Food and Drug Administration (FDA) for contraception for up to 5 years and for heavy menstrual bleeding. There is no FDA warning for VTE risk on the package insert.

Multiple studies have evaluated use of the 52-mg LNG-IUS and VTE risk in a low-risk population. The largest was a 2009 national registry cohort study in Denmark involving non-pregnant women aged 15 to 49, with no history of cardiovascular disease or malignancy. The study evaluated 10.4 million woman-years and reported 4,214 VTE episodes. The authors concluded that compared to non-use of hormones, use of the 52-mg LNG-IUS was not associated with increased risk of VTE (RR 0.90; 95% CI 0.64–1.26). Two systematic reviews were conducted, one prior to and one including this article, both of which concluded that the 52-mg LNG-IUS does not increase VTE risk in low-risk populations.

The relationship between the 52-mg LNG-IUS and VTE risk has also been evaluated in populations at higher VTE risk. A 2016 systematic review included nine studies of the device in high-risk women with SLE, hypertension, smoking, thrombophilia, and history of VTE. The study concluded that there was no statistically significant increased risk of VTE in women using the 52-mg LNG-IUS in these high-risk populations.

Patient #2: DMPA
A 21-year-old G0P0 presents with amenorrhea for 6 months using intra-muscular (IM) DMPA, which was started for menorrhagia. She is not sexually active and tells you "I don’t want a foreign object in my body." Her friend was recently diagnosed with deep vein thrombosis after a car accident and leg fracture. Although your patient doesn’t have any other personal risk factors for VTE, she is concerned about her own VTE risk on an upcoming trip while using DMPA.

You counsel your patient that a meta-analysis that found no increased VTE risk with other progestin-only agents did find a doubling in VTE risk with DMPA use. Despite this increased relative risk, the baseline risk of VTE is 1 to 10 per 10,000 yearly in a young, healthy population, so her absolute risk of VTE remains low on the order of 2 to 20 per 10,000. MEC guidelines are category 2 (benefits generally outweigh risks) for DMPA use in women with current VTE, history of VTE, or risk factors for it. You discuss with your patient that estrogen-containing options including COC pills would also be an option for her, however, they increase VTE risk 3-5 fold, which is a greater risk compared to progestin-only agents.

LITERATURE
Injectable DMPA is FDA-approved for prevention of pregnancy at a dose of 150 mg IM every 3 months. Contraindications listed on the package insert include active VTE and history of VTE.

A 2012 Dutch metaanalysis in women at low risk of VTE found no increased risk of VTE among overall users of a progestin-only contraceptive compared to non-users (relative risk 1.03; 95% CI 0.76 to 1.39). Importantly, the subgroup analysis of DMPA users demonstrated that, unlike other progestin-only options like the LNG-IUS and norethindrone, DMPA was associated with a doubling in VTE risk compared to non-users of hormones (relative risk 2.67; 95% CI 1.29 to 5.53).

Two studies assessed VTE risk with DMPA use in populations at higher VTE risk. The first found a trend toward an increased risk of VTE in smokers using DMPA (OR 7.0; 95% CI 0.4–138) compared to smokers not using hormones (OR 1.3; 95% CI 0.97–1.6), however, the confidence intervals were wide and the results were not statistically significant. The second is a case control study of women with Factor V Leiden mutations, which found no increased risk of VTE in women using other progestin-only agents, however, an increased risk of VTE was found in users of DMPA (OR 2.2; 95% CI 1.3-4.0).
Patient #3: Norethindrone acetate

A 41-year-old G3P3 with a tubal ligation, migraine with aura, depression, and VTE during her third pregnancy presents to the Emergency Department with regular heavy menstrual bleeding. She has been bleeding for 5 days and is hemodynamically stable with moderate continued bleeding and a hemoglobin of 9.2 g/dL.

You counsel your patient that due to her migraine with aura and history of VTE, estrogen-containing medications are not an option for her (MEC category 4, unacceptable health risk with method). However, for a rapid response and amenorrhea, contraceptive dosing of progestins may not be adequate. Available evidence shows that contraceptive doses of norethindrone acetate (0.35 mg) do not increase VTE risk. However, VTE data on higher doses of norethindrone acetate 2.5 mg to 15 mg commonly used for AUB are less clear. Your patient elects to start norethindrone acetate 2.5 mg and you both agree to start with the lowest dose that controls her bleeding. You schedule follow-up in your clinic to discuss longer-term options including the LNG-IUS and endometrial ablation.

**LITERATURE**

Norethindrone acetate is FDA-approved for contraception at a dose of 0.35 mg, and for secondary amenorrhea, endometriosis, and AUB at a dose of 5 to 15 mg. The FDA does list “active deep vein thrombosis, pulmonary embolism or history of these conditions” as a contraindication for use of the higher doses of norethindrone but not for the contraceptive dose.

## TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Levonorgestrel IUS (Mirena, Skyla, Kyleena, Liletta)</th>
<th>Medroxyprogesterone acetate (Provera)</th>
<th>Norethindrone acetate (Aygestin, Micronor)</th>
<th>Megestrol acetate (Megace)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contraception</strong></td>
<td></td>
<td></td>
<td>0.35 mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>AUB</strong></td>
<td></td>
<td>150 mg IM q3 months</td>
<td>5-15 mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td></td>
<td>5-10 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FDA VTE warning</strong></td>
<td>No FDA warning</td>
<td>Contraindications: active VTE and history of VTE</td>
<td>Contraindications: active VTE and history of VTE (5-15 mg only)</td>
<td>Advanced carcinoma of the breast or endometrium; treatment of cachexia in patients with AIDS; used off-label for AUB.</td>
</tr>
<tr>
<td><strong>MEC category</strong></td>
<td>2 (injectable)</td>
<td>2 (injectable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History of VTE</strong></td>
<td>2 (injectable)</td>
<td>2 (0.35 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thrombogenic</strong></td>
<td></td>
<td>2 (0.35 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mutation</strong></td>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evidence for risk of VTE</strong></td>
<td>No increased risk in low- and high-risk populations.</td>
<td>DMPA doubles risk in low-risk women and increases risk on women with FVL mutations. Limited research on oral dosing used for AUB.</td>
<td>No increased risk with contraceptive dosing. Limited research on higher doses used for AUB.</td>
<td>Increased risk of VTE in inherently high-risk population (i.e. nursing home patients, advanced malignancy)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AUB, abnormal uterine bleeding; DMPA, depot-medroxyprogesterone acetate; FDA, Food and Drug Administration; FVL, factor V Leiden; IM= intramuscular; IUS, intrauterine system; MEC, medical eligibility criteria; VTE, venous thromboembolism.
Several large studies on norethindrone acetate 0.35 mg used for contraception conclude that there is no increased risk of VTE with this dose.8-10 However, there are no studies on VTE risk with the higher doses of the drug used to manage AUB. Interestingly, a small study measured in vivo conversion of norethindrone acetate to ethinyl estradiol and concluded that 20 mg of norethindrone acetate may be equivalent to taking a pill containing 30 mcg of ethinyl estradiol.16 Prior small studies had varied results, with one suggesting no clinically significant conversion,17 another suggesting significant conversion at higher doses of norethindrone acetate,18 and a third suggesting rates of conversion of 6 µg ethinyl estradiol per 1 mg norethindrone acetate which could be significant based on dose.19 The in vivo impact of this conversion on VTE risk has not been evaluated, however, these findings could have implications for the VTE risk of the higher doses of norethindrone acetate used for AUB.

Oral medroxyprogesterone acetate is also used for AUB management at a dose of 5 to 10 mg, and is an option in this scenario. Little research has been done on VTE risk with oral medroxyprogesterone acetate in premenopausal women. A single relevant study was identified that included low-risk patients taking oral Provera; there was no association between VTE and progestin-only agents including oral medroxyprogesterone acetate, however, the size was small.20 Clearly, this is an area where more research is needed.

**Patient #4: Megestrol acetate**
DD is a 52-year-old G2P2 obese, perimenopausal hypertensive and diabetic woman with irregular heavy bleeding. You perform an in-office endometrial biopsy, which demonstrates disordered proliferative endometrium. She is started on norethindrone acetate 5 mg daily, increased to 15 mg, however, she continues to bleed heavily.

You counsel your patient that some data, mostly from small studies in patients with active malignancy using MA in varying doses, did show a small increased VTE risk. However, these study populations are at inherently higher risk for VTE and may not be representative of this woman’s personal risk. There is very limited research on megestrol acetate for AUB.

**LITERATURE**
Megestrol acetate is FDA-approved in doses of 40 to 320 mg/day for palliative treatment of advanced carcinoma of the breast or endometrium and treatment of cachexia in patients with AIDS.21 Regarding VTE risk, the FDA states that “thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.”21

Megestrol acetate is clinically used off-label for AUB, however, there are few data on this use. A retrospective chart review of 49 patients with AUB suggested efficacy of megestrol acetate in decreasing mean days of bleeding.22

A 2013 Cochrane review evaluating 1,602 patients using megestrol acetate for treatment of cachexia in patients with cancer, AIDS, and other pathologies found an increased relative risk of VTE of 1.84 (1.05-3.18).23 Four studies have focused specifically on MA and VTE risk, including a retrospective case control study of 435 women with cancer using megestrol acetate as an appetite stimulant, a retrospective descriptive study in nursing home residents, a cohort study in 97 patients with advanced cancer receiving chemotherapy, and a randomized study of 179 patients with breast cancer patients whose disease failed to respond to tamoxifen.27 Three of these small studies suggest an increased risk of VTE with megestrol acetate use with odds ratios ranging from 3.4 to 12.2.27 Because these studies all focused on patients at inherently higher risk of VTE, however, the results have very limited generalizability to a population of premenopausal women.

**Conclusions**
This review demonstrates the complexities of treating women with progestins for AUB. Shared decision-making between clinicians and their patients is indicated using the available data. The current data, clinical use, and expert opinion are often contradictory. This highlights the need for additional research on VTE risk of progestins used for management of AUB, especially in the context of other common risk factors for VTE, such as obesity, older age, and smoking.

FOR REFERENCES VISIT contemporaryobgyn.net/ProgestinsVTE
Menopausal symptoms through the seasons

by BEN SCHWARTZ

Like some aspects of reproductive function, menopausal symptoms appear to exhibit seasonal variation, according to new research from Menopause: The Journal of the North American Menopause Society. The study assessed the impact of season and proximity to the final menstrual period (FMP) on frequency of symptom reporting.

The authors included 955 participants from the Study of Women’s Health Across the Nation, a cohort study that followed a multiethnic sample during the transition from premenopause to postmenopause over a 10-year period. Participants filled out menstrual calendars daily to capture days when spotting or bleeding occurred. Women answered questions about hormone therapy (HT) use and gynecological procedures that could affect their bleeding reports monthly and also completed a short survey about whether they had experienced symptoms (hot flashes, night sweats, and trouble sleeping) in the past month.

FMP was defined as the first day of the bleeding episode that was followed by at least 12 months of amenorrhea. Hot flashes, night sweats, and trouble sleeping were coded as a binary variable (yes/no) for each month of observation. HT use varied by time and was coded based on current use (yes/no) for each month of observation.

The authors found that 5 to 10 years before the FMP, approximately 20% of women reported hot flashes and night sweats. During that period, approximately 40% reported trouble sleeping. These numbers rose approximately 4 years before the FMP with a sharp jump in prevalence of hot flashes (~60%) and night sweats (~40%) coincident with the FMP.

In terms of seasonality, the authors noted that a peak in hot flash reports was observed in July, while January had a trough in hot flash reports. Women had 66% greater odds of a hot flash at their seasonal peak compared to their seasonal minimum in both the unadjusted model and the model adjusted for smoking, race, age at FMP, and body mass index. The corresponding odds for night sweats and sleep problems were 50% and 24%, respectively. The authors also noted that odds of reporting all three symptoms increased as women approached the FMP.

The authors believe their findings indicate that menopausal symptoms exhibit seasonal variation based on summer and winter. They believe their findings indicate the need for physicians to recognize the summer months as a critical period for managing their patients’ symptoms.

**Ben Schwartz** is the associate editor for Contemporary OB/GYN.

**SOURCE**

---

Premature menopause and CVD
Women who reach menopause before 40 may have an increased risk for subsequent cardiovascular disease, [contemporaryobgyn.net/MenopauseCVD](http://contemporaryobgyn.net/MenopauseCVD)

Practical approach to managing menopause
HT is not without controversy, but it is still one of the most effective treatments for patients with symptoms. [contemporaryobgyn.net/ManagingMenopause](http://contemporaryobgyn.net/ManagingMenopause)
Intrauterine devices are safe and effective—yet underutilized. Explore the IUD Provider Toolkit for authoritative information on this long-acting form of contraception from professional, government, and nonprofit organizations.

Go to: contemporaryobgyn.net/iud-toolkit
Does powder increase risk of ovarian cancer?

by JUDITH M. ORVOS, ELS

Experience in more than a quarter million women shows no significant association between use of powder in the genital area and ovarian cancer. The findings, published in JAMA, are from the largest study to date on this topic.

The conclusion was drawn by researchers based on a pooled analysis of data from four large, US-based cohorts: Nurses’ Health Study (NHS), Nurses’ Health Study II (NHSII), Sister Study (SIS), and the Women’s Health Initiative Observational study (WHI-OS). The goal was to determine if there was a link between ever use of powder in the genital area and self-reported incident ovarian cancer. The new report includes updated data, more cases, and longer follow-up than the original research.

The authors noted that in the four studies, participants were asked about use of powder in the genital area in different ways. They therefore harmonized the data by categorizing the participants as having ever used or never users. Long-term use was defined as at least 20 years or use at ages 10 to 13 years and also in the last year. Women were frequent users of powder if they had used in the genital area at least once a week, at least once a week in the last year, or “frequently” from ages 10 to 13.

Confounders in the four studies also were harmonized and included age at baseline, race, education, body mass index, parity, smoking status, hormone therapy use, and tubal ligation, hysterectomy, and menopausal status.

Across the studies, 39% of women commonly used powder in the genital area, with 53% ever use in WHI-OS, 41% in NHS, 27% in SIS, and 26% in NHSII. Rates of long-term use were 16% in WHI-OS and 6% in SIS and NHSII. Frequent use was reported by 27% of the women in NHS, 26% in NHSII, and 7% in SIS. The authors said that “there appeared to be a generational trend in use of powder in the genital area, with older cohorts more likely to report use.” Users of powder also were more likely than non-users to be black (6% vs 3%), obese (26% vs 19%), and to be hysterectomized (22% vs 18%), and less likely to have used oral contraceptives (57% vs 64%).

Looking at incidence of ovarian cancer in the pooled sample, the authors found that among ever users, it was 61 cases per 100,000 person years versus 55 cases per 100,000 person years in women who had never used powder on their genital area. At age 70, the estimated risk difference was 0.09% (95% CI, -0.02% to 0.19%) and the estimated hazard ratio (HR) was 1.08 (95% CI, 0.99 to 1.17). The estimated HR for frequent vs never use was 1.09 (95% CI, 0.97 to 1.23) and for long-term vs never use, was 1.01 (95% CI, 0.82 to 1.25).

The researchers conducted subgroup analysis for 10 variables and none of the tests for heterogeneity were statistically significant for any of the comparisons. The estimated HR for the association between ever use of powder and ovarian cancer risk in women with a patent reproductive tract was 1.13 (95% CI, 1.01 to 1.26) but the P value for interaction comparing women with vs. without patent reproductive tracts was 0.15.

Commenting on how powder might affect reproductive organs, the authors said that their analysis and a possible positive association in women with patent reproductive tract “lends support to the hypothesis that powder with or without asbestos could irritate and inflame the reproductive tract.” They emphasized, however, that the finding should be considered exploratory and hypothesis generating. While concluding that their study showed no statistically significant association between self-reported use of powder in the genital area and incidence of ovarian cancer, they also acknowledged that it was underpowered to identify a small increase in risk.

Judith M. Orvos is an editorial consultant for Contemporary OB/GYN.

SOURCE
Too many teen pelvic exams and Pap tests?

by JUDITH M. ORVOS, ELS

Results of a nationally representative study indicate that many young women receive bimanual pelvic exams (BPEs) and Pap tests that may be unnecessary, and not in compliance with the latest guidance from the American College of Obstetricians and Gynecologists (ACOG).

ACOG notes that for an adolescent reproductive health visit, an internal pelvic exam may be appropriate if issues such as abnormal bleeding or discharge, or abdominal or pelvic pain is a concern, but that an adolescent may visit a gynecologist several times before a biannual exam is needed. If a speculum or bimanual exam is indicated, a thorough explanation should always precede the procedure. Patients can find information about a gynecologic visit in the ACOG FAQ document, “Your First Gynecological Visit (Especially for Teens).” Pap tests are not recommended until age 21.

Published in JAMA Internal Medicine, the new findings are from a cross-sectional analysis of the National Survey of Family Growth (NSFG) from September 2011 through September 2017 focused on a population-based sample of young women aged 15 to 20 years. The main outcomes were receipt of a BPE or a Pap test in the last 12 months and the proportion of potentially unnecessary examinations and tests.

Of the young women surveyed, 4.8% were pregnant, 22.3% had undergone testing for a sexually transmitted infection (STI) and 4.5% received treatment or medication for an STI in the past 12 months.

Only 2.0% reported using an intrauterine device (IUD) and 33.5% used at least one other type of contraception in the past 12 months.

Having a BPE was associated with having a Pap test (adjusted prevalence ratio [aPR] 7.12; 95% CI, 5.56 to 9.12), testing for STIs (aPR 1.60; 95% CI, 1.34 to 1.90) and using hormonal contraception other than an IUD (aPR 1.31; 95% CI, 1.11 to 1.54). It was also associated with being older (aPR 1.25; 95% CI, 1.08 to 1.45). Young women who had a Pap test were seven times more likely to also report receiving a BPE (aPR 7.12; 95% CI, 5.56 to 9.12). Using hormonal contraception other than an IUD was associated with a 31% higher risk of receiving a BPE than in women who did not use those forms of contraception. This is in spite of ACOG’s clear statement that “A pelvic examination is not necessary before initiating or prescribing contraception, other than an intrauterine device, or to screen for STIs.”

Looking at the impact of insurance, the authors found that young women with public or no insurance were less likely to receive a BPE than those with private insurance. Race/ethnicity and STI treatment were not found to be associated with having a BPE when adjusting for other covariates.

Among US young women aged 15 to 20 years surveyed in the years 2011 to 2017, approximately 2.6 million reported having received a BPE in the last 12 months. The authors estimated that more than half (54.5%) or 1.4 million of those exams may have been unnecessary. An estimated 1.6 million of the women, the researchers say, may have had an unnecessary Pap test during the same period.

Based on the results of their analysis and assuming that a Medicare payment for a screening BPE of $37.97 and for a screening Pap test of is $44.78, as was the case in 2014, the authors estimate that the potentially unnecessary BPEs and Pap tests would have cost more than $123 million in 1 year.

Commenting on the findings, the researchers concluded that they “suggest the need for education for health care professionals, parents, and young women themselves to improve awareness of professional guidelines and the limitations and harms of routine pelvic examination and Pap test and to ensure that these tests and examinations are performed only when medically necessary among young women.”

Judith M. Orvos, ELS, is an editorial consultant for Contemporary OB/GYN.

SOURCE
Hypertension is a primary contributor to cardiovascular disease (CVD), which is a major cause of death in women. Traditionally defined as an average blood pressure of at least 140/90 mm Hg or use of antihypertensive medication, hypertension affects about 30% of US adults aged 18 or older. While the 140/90 mm Hg cut-off is used in the 2004 Joint National Commission (JNC) report on hypertension, more recently, the American College of Cardiology and the American Heart Association (ACC/AHA) recommended lowering the defining blood pressure for hypertension to 130/80 mm Hg. According to the new ACC/AHA guidelines, stage I hypertension is diagnosed by a systolic blood pressure of 130 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg. A blood pressure of ≥ 140 mm Hg systolic or 90 mm Hg diastolic defines stage II hypertension. Blood pressure should be taken by trained personnel who ensure that the patient has been at rest and seated in a chair with feet on the floor and has an empty bladder. A properly sized cuff encircles 75% to 100% of the patient’s arm. The diagnosis can be made by averaging at least two readings on at least two separate occasions using readings from ambulatory blood pressure monitoring, home self-monitoring, and/or a follow-up visit. The American College of Obstetricians and Gynecologists (ACOG) acknowledges the new, lower diagnostic threshold for hypertension in its bulletin on chronic hypertension in pregnancy and recommends that patients diagnosed with hypertension using these values be managed in pregnancy using the guidelines for chronic hypertension. However, because ACOG adheres to the JNC cutoff in its definition of gestational hypertension, and given that the data currently available utilize the 140/90 threshold, we will also utilize the 140/90 cutoff in this article.

Among women, prevalence of hypertension rises from 10% in the 20- to 44-year-old range to 78% by age 75. Significant disparities exist in medical treatment of hypertension. Approximately half of all adults (53.5%) and 52.1% of women have uncontrolled hypertension. Hypertension is more common among black adults (38.6% prevalence) and is less likely to be treated in this population. Women aged 18 to 39 are less likely than older women to

**Tips for counseling hypertensive patients**

This installment of our Complex Contraceptives series examines contraception considerations for patients with high-blood pressure.

by **CHARISSE M. LODER, MD, MSC, AND LAUREN OWENS, MD, MPH**

**DR LODER** is a Clinical Assistant Professor at Michigan Medicine, University of Michigan, Ann Arbor.

**DR OWENS** is a Clinical Assistant Professor at Michigan Medicine, University of Michigan, Ann Arbor.
have controlled hypertension, potentially predisposing women in this age group to pregnancy complications related to their hypertension. In addition, people who are Mexican-American, lack a usual medical care site, receive medical care less than twice per year, or lack health insurance are less likely to receive medical treatment for hypertension than other people with hypertension. Moreover, groups already at disproportionate risk of adverse pregnancy outcomes, such as black women and women lacking health insurance, are more likely to experience complications of hypertension. Given that many reproductive-aged women choose to receive their primary healthcare through their ob/gyn, there is an opportunity to diagnose, counsel on, and treat hypertension during the health maintenance exam. We have opportunities to engage in innovative patient-centered management of hypertension before, during, and after pregnancy to reduce disparities.

Hypertension medication and pregnancy

Lifestyle modifications such as weight loss (for overweight or obese patients), a heart-healthy diet, sodium reduction, increased physical activity, and limitation of alcohol consumption are recommended for first-line management of hypertension. The first-line pharmacologic classes of antihypertensives are thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers. However, among women seeking pregnancy or who are currently pregnant, the preferred antihypertensive medications are methyldopa, nifedipine, and/or labetalol per the ACC/AHA. In clinical practice, methyldopa is less frequently used; per ACOG, it is less effective in the control of chronic hypertension and more likely to have side effects (drowsiness, headache, orthostatic hypotension). Women with hypertension should not be treated with ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors in pregnancy because of the risk of fetal renal damage. Exposure to these medications in the second and third trimesters is most concerning because of the risk of impaired fetal kidney function leading to oligohydramnios, which may in turn impair lung development. Data are less clear regarding exposure risk in the first trimester; however, most studies show a slight increased risk in congenital malformations with medications affecting the renin-angiotenin-aldosterone system.

Hypertension sequelae

Hypertension is a risk factor for CVD, which itself is the top cause of death in the United States. Cardiovascular disorders are a top cause of maternal mortality in the United States and hypertensive disorders of pregnancy are specifically responsible for 9.4% of maternal deaths. Patients with a history of

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>US MEC Recommendations for contraceptive use in women with hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sub-condition</strong></td>
<td>Cu-IUD</td>
</tr>
<tr>
<td>A) Adequately controlled hypertension</td>
<td></td>
</tr>
<tr>
<td>B) Elevated blood pressure levels:</td>
<td></td>
</tr>
<tr>
<td>i) Systolic 140-159 mm Hg or diastolic 90-99 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>ii) Systolic ≥160 mm Hg or diastolic ≥100 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>C) Vascular disease</td>
<td></td>
</tr>
</tbody>
</table>


Abbreviations: Cu-IUD = copper intrauterine device; CHC = combined hormonal contraception; DMPA = depot medroxyprogesterone acetate; LNG-IUS = levonorgestrel intrauterine system; POP = progestin-only pill; US MEC = U.S. Medical Eligibility Criteria
preeclampsia have quadrupled the risk of developing chronic hypertension.8

Impact on pregnancy
Although most people with hypertension have no associated complications in pregnancy, hypertension is associated with increased risk for adverse health events as a result of pregnancy. In particular, chronic hypertension is associated with increased risk of gestational diabetes, postpartum hemorrhage, planned cesarean section, and preeclampsia.4 Given the increased risk of preeclampsia, women with chronic hypertension should initiate low-dose aspirin daily prior to 16 weeks’ gestation for preeclampsia prophylaxis per ACOG and the US Preventive Services Task Force.6 Chronic hypertension also carries fetal risks; growth restriction, stillbirth, and preterm birth are more common in pregnancies exposed to chronic hypertension.4 Both treated and untreated hypertension are associated with an increase in fetal congenital heart defects (RR 2.95% CI [1.5-2.7] and RR 1.4, [1.2-1.7] respectively).10

Contraception and hypertension
In the following segments, we discuss the safety of various forms of contraception for people with different types of hypertension. Contraceptive counseling should be patient-centered, taking into account a woman’s reproductive health goals and desires. Providers should consider a patient’s blood pressure control and overall cardiovascular health when discussing the risks and benefits of contraceptive methods as compared to the risks of an unintended pregnancy. Please note that the safety profiles mentioned here assume that the patient has no other comorbidities affecting the safety and suitability of these methods.

We recommend a useful tool, the US Centers for Disease Control and Prevention’s Medical Eligibility Criteria (US MEC), which provides guidelines surrounding the safety of contraceptive methods for a range of given medical conditions. We have used these recommendations to inform our discussion of contraceptive methods for women with hypertension. It is important to note that the US MEC states that patients with hypertension and systolic pressures ≥ 160 mm Hg or diastolic pressure ≥ 100 mm Hg are at increased risk of adverse health events with pregnancy. As such, providers should take contraceptive efficacy into account when counseling patients. US MEC categories 1 and 2 indicate that a contraceptive method is safe and without restrictions for the specific medical condition and the advantages of the method generally outweigh any theoretical risks, respectively. Meanwhile, contraceptive methods in categories 3 and 4 should be avoided. Category 3 suggests that the theoretical or proven risks of the contraceptive method outweigh the benefits. Category 4 means that there is an unacceptable risk to the patient with use of the contraceptive method.11 US MEC recommendations for hypertensive disease and contraceptive are presented in Table 1.

Estrogen and hypertension
Estrogen therapy should be avoided in those with hypertension because it increases blood pressure while also increasing the risks of myocardial infarction and ischemic stroke.12 These relationships are thought to be dose-dependent, with higher doses of ethinyl estradiol posing a greater risk of CVD when compared to lower doses. Estrogen is theorized to activate the renin-angiotensin system and can increase systolic blood pressure by an average of 8 mm Hg.13

The US MEC states that combined hormonal contraception (CHC) poses an increased risk (category 3) for those with hypertensive disorders.14 For those with systolic blood pressure ≥ 160 mm Hg or diastolic ≥ 100 mm Hg, the risks outweigh the advantages. Additionally, the US MEC states that...
are unacceptable risks in using CHC in those with blood pressures above 160/100 (category 4). It is important to note that even those with blood pressure that is well-controlled with anti-hypertensives are still at increased risk for CVD with estrogen use.\textsuperscript{11}

**Progestin methods**

Progestin methods are generally considered safe in patients with hypertension. For patients with adequately controlled hypertension, progestin-only pills (POPs), etonogestrel implants, and hormonal intrauterine devices are US MEC category 1. Injectable progestin contraception, depo medroxyprogesterone acetate (DMPA) is category 2, meaning that its advantages generally outweigh theoretical or proven risks. These categories hold for patients without a formal diagnosis of hypertension who have elevated blood pressure measurements < 160 mm Hg systolic or < 100 mm Hg diastolic. However, the risk/benefit balance tips when we consider use of DMPA for patients with a systolic blood pressure $\geq 160$ mm Hg or diastolic blood pressure $\geq 100$ mmHg with patients who have vascular complications from hypertension. For these patients, DMPA is US MEC category 3 and all other forms of progestin are category 2. In addition, some data show that DMPA increases lipid levels with long-term use; therefore, patients with multiple risk factors for CVD—including hypertension, hyperlipidemia, diabetes, smoking, and obesity—should avoid using injectables.\textsuperscript{15}

**Nonhormonal methods**

Nonhormonal methods such as behavioral methods, condoms, withdrawal, the copper intrauterine device (IUD) and permanent contraception via (partial) salpingectomy or vasectomy are safe for hypertensive patients. Regardless of the type of hypertension, the copper intrauterine device (IUD) is US MEC category 1.\textsuperscript{11} Although the copper IUD and permanent contraception have failure rates less than 1%, these other nonhormonal methods have higher failure rates and patients who choose to use barrier and behavioral methods of contraception should be informed of the failure rates of these methods in typical use. The US MEC notes that long-acting reversible contraceptives like IUDs and implants may be the best choice for patients with hypertension, likely due to their high efficacy and good safety profiles. While those are important considerations, so are a patient’s values and preferences for a contraceptive method. However, it is important to keep in mind that when weighing the risks of contraception that the alternative is potential pregnancy with its own set of risks and benefits. Shared decision-making with patients using validated tools for reproductive life planning and patient-centered guidelines for communication\textsuperscript{16} (Table 2) can improve patient satisfaction with contraceptive care.

---

**CASE**

A 34-year-old G2P2 presents to the office for her well-woman exam. She reports being in general good health. However, her primary care physician has been “keeping an eye on her blood pressure,” which was 142/78 at the woman’s last check-up. The only medication she is currently taking is an oral contraceptive pill. She is happy with this method and is considering a pregnancy in the next 6 months. Her blood pressure is 164/100.

**WHICH STATEMENT BELOW IS CORRECT?**

A. You recommend treating her hypertension and keeping her contraceptive method.

B. You recommend switching to a POP method of contraception, given the patient’s expressed preferences for pregnancy timing and medical history.

C. You recommend switching to the progestin injectable.

**ANSWER B**

**Case discussion**

According to the ACC/AHA guidelines, this patient has stage 2 hypertension.\textsuperscript{3} As such, the risks of estrogen-containing contraceptive methods likely outweigh the benefits. If this patient is taking an antihypertensive medication, she is not a good candidate for estrogen-containing methods such as CHC. Although an injectable contraceptive would be safe for this patient despite her hypertension, her fertility desires make it a less ideal method. Given that she may want to conceive in the next year, the delayed return to fertility that DMPA can cause also makes it a less ideal method for her. The POP is safe in regard to this patient’s hypertension and allows for the quick return of fertility when she decides to pursue pregnancy.
the plaintiff for a mesh sacral colpopexy, but that intraoperatively, Dr. B decided against the use of mesh.

A review of systems and physical exam were generally within normal limits except that the exterior vaginal wall demonstrated a large cystocele to 1 cm past the introitus, cervix at the level of the introitus, and there was a large rectocele. Bedside cystometrics was also performed and demonstrated a fair sensation at 100; fullness 270, max capacity at 300 with a negative cough stress test, pretest postvoid residual (PVR) of 180, and post-test residue of less than 10. Dr. C’s overall impression was that the plaintiff had a large recurrent prolapse, status post-uterosacral ligament suspension.

Dr. C indicated he had a “long discussion” with the plaintiff. He noted that uterosacral ligament suspensions have a success rate at best in the range of 60% to 80%. Sacral colpopexy would give her a success rate of close to 99%. His note also indicated that the plaintiff would consider having a sacral colpopexy as well as anterior and posterior repair. Dr. C also indicated that he took time to discuss the pros, cons, risks, benefits, success and failure rates of the proposed procedure as well as anterior and posterior repair. Dr. C also indicated that he took time to discuss the pros, cons, risks, benefits, success and failure rates of the proposed procedure as well as complications including but not limited to injury to bowel, urinary tract infection (UTI), blood loss, mesh erosion, new onset of incontinence, urinary retention, and need for additional surgery.

The plaintiff’s treatment with Dr. A began on June 2, 2014. At that time, she was evaluated for symptomatic vaginal prolapse for the past 10 months, which was affecting her lifestyle. Her current complaint was voiding 15 to 20 times per day and twice per night. Dr. A’s conclusion was vaginal vault prolapse post-hysterectomy.

Options of conservative observation, pessary placement, and surgery were discussed in detail. Potential risks and complications were also discussed. The plaintiff agreed to undergo a minimally invasive sacrocolpopexy.

On July 14, 2014, the plaintiff underwent a Pelvic electromyogram (EMG) and cystometrics, which showed that her bladder capacity was normal with sphincter coordination. There was urethral hypermobility with SUI. The plaintiff returned to Dr. A’s office on August 18, 2014, and Dr. A suggested a laparoscopic vs. robotic sacrocolpoplasty with midurethral sling. The plaintiff had Stage 3 anterior wall vaginal prolapse (AWVP) and Stage 2 apical prolapse and underwent urethrosacral culpoplasty with Ethibond and Vicryl without sacrocolpopexy, anterior repair perineorrhaphy, supracervical hysterectomy, and BSO in May 2013. Comorbidities included hypertension, diabetes mellitus, hypothyroidism, gastroesophageal reflux disease, and atherosclerosis. She was postmenopausal.

Dr. A documented an exhaustive discussion with the plaintiff regarding the potential risks and complications of the proposed surgery, which included, among other things, risk of infection requiring antibiotics and rehospitalization, and risk of damage to adjacent organs including but not limited to the bladder, bowel, ureters, and nerves. The plaintiff also signed a general surgery consent form acknowledging that Dr. A explained the potential risks of the procedure in a way that the plaintiff could understand.

On September 3, 2014, the plaintiff presented to Defendant Hospital for surgery. The procedure performed was diagnostic laparoscopy with lysis of adhesions, sacrospinous ligament fixation, anterior repair, laparotomy, enterotomy repair x 2 and cystoscopy. Laparoscopic findings included dense adhesions noted between the small bowel and anterior abdominal wall extending from the umbilicus to the bladder. The adhesions penetrated into the fascia consistent with a ventral hernia and involved the rectal muscle. There were also adhesions between the colon and lateral sidewalls and the small bowel and bladder. Lysis of adhesions was performed for 1.5 hours. A questionable (non-circumferential) partial rectal prolapse was encountered. Cystoscopy revealed proper positioning of the mesh without perforation or ureteral obstruction. An Obtryx sling material was used.

Cystometrics showed pretest and post-test PVRs of 180 and < 10, respectively.
According to Dr. A’s operative report after the abdominal cavity was surveyed:

“Dense adhesions were noted along the anterior abdominal wall between the small bowel, the omentum, and the anterior abdominal wall. Careful dissection was performed with the monopolar scissors mostly without heat, to lyse the adhesions for about 1.5 hours. During this dissection, as we uncovered the adhesions, we discovered that the bowel was densely adhered to the anterior abdominal wall fascia and rectus muscles. Also a 3 mm serosal tear was noted in the small bowel. This was tagged with a vicryl and colorectal was consulted. He agreed this needed oversewing and further lysis of adhesions and that this would be best achieved via an open incision. We converted to a midline incision (chosen based on where the adhesions were). The abdomen was insufflated as we made an incision with the knife and carried it down to the underlying layer of fascia to help protect the bowel. At this point we connected the incision with the ventral midline hernia just inferior to the umbilicus and entered the peritoneal cavity. We extended the incision inferiorly taking care to avoid the bowel adhesions. At this point colorectal surgery scrubbed in and in running the bowel an enterotomy was identified with no frank spillage and he primarily repaired that with vicryl and then oversewed the previously identified serosal tear. He also assisted with the remaining lysis of adhesions.

At this point, the decision was made to not proceed with the sacrocolpopexy due to the concern for a contaminated field. The plaintiff was admitted to the Defendant Hospital with complaints of mild soreness at the incision site. However, she was afbrile, voided, and tolerated liquids. She was then discharged home on Oxycodone, Motrin and Senna. She was instructed to continue all prior medications. No antibiotics were prescribed.

The plaintiff followed up with Dr. A’s office on September 9, 2014. She reported that she was voiding, had a bowel movement, and was ambulating. On September 13, 2014, the plaintiff was admitted to the Defendant Hospital with complaints of oozing from the vaginal incision site. Her vital signs were stable and she was afbrile with a pain score of 5/10. She reported 2 days of peri-incisional erythema and separation of the incision on the day of admission. She had called Dr. A’s office and Keflex was prescribed for presumed cellulitis.

The plaintiff had a visible 2-cm abdominal wall incision with 10-cm tunneling above the fascia. Purulent drainage was expelled, drained, and debrided and the wound was packed while in the emergency room. The plaintiff was admitted for wound infection and was started on wet-to-dry dressing changes, Ancef, and Bactrim. Over the next 2 days, her erythema decreased with dressing changes and Gram stain of the drainage showed neither white blood cells nor bacteria. Cultures showed moderate Staph Aureus. The dehiscence was noted to be 2.5 cm deep to fascia and 1.5 cm wide. However, the plaintiff remained afbrile without evidence of sepsis. She was discharged home on September 16, 2014 on oral clindamycin.

On September 22, 2014, the plaintiff was seen by Dr. A after being hospitalized for a wound infection. However, the wound was slowly healing and measured 3 cm deep with some tracking superiorly. Dr. A noted that the plaintiff had no complaints of fever, chills, bulge or incontinence. She was to follow-up in 2 weeks, at which time a pelvic exam would be done.

On September 26, 2014, VNS called Dr. A’s office and reported that there was yellow-green discharge from the wound. However, there was no odor, increased drainage or fever. An office appointment was arranged for the next Monday. The plaintiff returned...
The plaintiff asserted injuries including large recurrent prolapse, urgent urinary frequency, nocturia, and loss of services to her husband.

to Dr. A on September 29, 2014 for a follow-up visit. At that time, her wound was examined and repacked. On October 6, 2014, the plaintiff was seen for a follow-up visit for her wound and for complaints of urinary frequency. At that time, it was noted that her wound was healing and was 2 cm deep and 3 cm long. At the next visit on October 20, 2014, Dr. A noted that the plaintiff’s wound was almost closed. No prolapse was appreciated on exam and estrogen cream was prescribed for atrophic vaginitis.

On October 27, 2014, the wound was noted to be closed and the plaintiff reported no pain or incontinence. At a follow-up visit on February 1, 2015, the plaintiff complained of double voiding and incomplete emptying; she was treated with Macrodantin. At her last reported visit with Dr. A, on March 16, 2015, she complained of rectal bulge (small hemorrhoid noted on rectovaginal exam), “occasional” fecal urgency and “some” incomplete bladder emptying. A bowel regimen was started and she was referred for pelvic floor exercises. On a form entitled “Patient Global Impression of Improvement,” the plaintiff indicated that her postoperative condition was “normal” and that when compared to her preoperative condition she was “much better.”

On July 28, 2015, the plaintiff presented to her private ob/gyn, Dr. E, with complaints of a recurrent prolapse. However, Dr. E’s note includes no exam findings consistent with recurrent prolapse. On November 16, 2015, the plaintiff underwent right carotid endarterectomy at Codefendant University Hospital, which was complicated by transection of the carotid artery. Postoperatively she had a right middle cerebral artery infarction with left hemiparesis. There was no reference to any urologic complaints.

Allegations
The plaintiff alleged that the defendants were negligent in performing a laparoscopy; in causing an enterotomy; in causing the need to perform an exploratory laparotomy and repair; in failing to properly and sufficiently plan the laparoscopy; in failing to perform appropriate preoperative testing to assess adhesions; and in failing to take all measures necessary to prevent any complications from the laparoscopy. Plaintiff argued the procedure should have been commenced open and opposed to laparoscopically. In addition, plaintiff contended Dr. B “botched” the first prolapse repair, leading to the cascade of events that necessitated future surgeries and complications.

As a result of the alleged negligence, the plaintiff asserted injuries including large recurrent prolapse, urgent urinary frequency, nocturia, and loss of services to her husband.

Discovery
The plaintiff testified that Dr. A advised her that when she started the procedure laparoscopically, they came into contact with numerous adhesions which no longer permitted her to perform the surgery as planned. In addition, as a result of the adhesions, her bowel was nicked and ultimately repaired intraoperatively. Since that surgery, she conceded she no longer experiences any type of urinary complaints.

In addition, with respect to the prolapse, the plaintiff also testified that following Dr. A’s surgery in September 2014, she no longer experienced any type of bulging or prolapse. She did testify that she had a brief recurrence in or about April of 2015, however, it self-resolved. With respect to the claim for loss of consortium, she testified that following her surgery with Dr. A, her ability to have a physical relationship with her husband was not affected. It was clear that any significant injury she suffered was related to the stroke she suffered in November of 2015.

Dr. B testified that one of the reasons why he decided to do the modified colpopexy, as opposed to the sacrocolpopexy, was because the plaintiff had diverticular disease. According to Dr. B, the plaintiff had a good postoperative course and as of the last time that he saw her, she had a normal vaginal vault and excellent apical suspension.

Dr. A testified that from the time of their first meeting, the plaintiff was insistent on having a sacrocolpopexy. She nevertheless went through a full presentation of the various options available to the plaintiff,
including pelvic floor therapy, placement of a pessary, and expectant management. The plaintiff refused those options. Alternative procedures discussed were colpocleisis; use of vaginal mesh; a vaginal approach using uterosacral ligament suspension; and sacrocolpopexy with mesh.

Upon entering the abdomen, Dr. A testified she encountered dense adhesions and, therefore, she called Colorectal Surgery to assist with the lysis of adhesions. She spent 1.5 hours lysing adhesions. At some point she noted a 3-mm serosal tear in the plaintiff’s bowel. Colorectal Surgery recommended that they convert to an open procedure in order to lyse adhesions and inspect the bowels. Both the serosal tear and the enterotomy were repaired with sutures. She cautioned the patient preoperatively about the risk of adhesions and conversion.

We had expert support from Obstetrics and Gynecology, Urogynecology and Colorectal Surgery as to the indications for surgery, the consent provided, the surgical approach and technique, as well as the conversion to open and repair of enterotomies, which were known risks of the procedure and could not be predicted or prevented by testing preoperatively.

**Result**

At the close of discovery, we moved for Summary Judgment (dismissal) as to our clients. So did counsel for Dr. B. Interestingly, the plaintiff’s counsel did not oppose our motions with an expert of his own, but instead tried to use our experts against each other to suggest that if sacrocolpopexy was not indicated when Dr. B operated, then it was a departure for Dr. A to perform that procedure. Alternatively, if it was indicated, then Dr. B departed by not performing it during the initial prolapse surgery. In reply, both defendants were able to use their experts to coordinate theories and display to the Court that there was no inherent contradiction between their respective positions. The Court did not accept the plaintiff’s arguments, found that defendants met their burden of proof entitling them to dismissal, and that the plaintiff’s failure to produce an expert affidavit in contravention of defendant’s positions was fatal to their claim.

**Analysis**

It can be tricky at times to coordinate defenses amongst codefendants whose treatment occurred at different stages of the patient’s care. Doing so, however, should be the primary objective, as a unified defense prevents the kind of blaming or finger-pointing that can weaken both defenses and lend weight and credibility to a plaintiff’s assertions. Here, both defendants were able to prove that their course of action at the time they undertook to treat the patient was appropriate, based upon not only the exercise of medical judgment, but the particular issues they were faced with respectively. Each physician was able to articulate their rationale for approach and decision-making in a way that enabled their retained experts to support their care, rather than blame the other for complications that proved to be known risks of surgery. Faced with a unified defense, the plaintiff could not find expert support for rebuttal.

Both defendants were able to prove that their course of action to treat the patient was appropriate.
MARKETPLACE

For Products & Services Advertising, contact: Joanna Shippoli
440-891-2615, jshippoli@mmhgroup.com

SEMINARS

EXAMPro
The Power to Pass
The OB/GYN Boards

PRACTICE AVAILABLE

LONG ISLAND, N.Y., OB/GYN AND PREGNANCY TERMINATION PRACTICE AND OFFICE AVAILABLE 3/2020

Stand-alone building houses 45-year solo OB/GYN and termination practice. Office rental includes the practice. Comes with state-certified ambulatory O.R. Ideal for practitioners doing ambulatory surgery.

Reply to: gynoman1@aol.com
631-724-6224

Reach your target audience.

Our audience.

Contact me today to place your ad.

Joanna Shippoli
(440) 891-2615
jshippoli@mmhgroup.com

ADVERTISER INDEX

Companies featured in this issue

To obtain additional information about products and services advertised in this issue, use the contact information below. This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.

CONTEMPORARY OB/GYN

MERCK AND CO INC
Nexplanon
www.nexplanon.com

THERAPEUTICS MD
Imvexxy
www.imvexxy.com

CONTEMPORARYOBGYN.NET
Find your work-life balance while leading a team as an OB/GYN Hospitalist Medical Director!

Put the passion back into practicing medicine by taking control of your time! Enjoy the freedom and flexibility of being an OB/GYN Hospitalist. Our unique OB/GYN Hospitalist model offers a work-life balance the traditional practice model can’t match.

We are seeking dynamic board certified OB/GYN physicians with a minimum of three years post-residency experience, active Florida state license and excellent communication skills to lead one of our practices in Central Florida.

**Facility Medical Director**  
Winter Haven Women’s Hospital  
Enjoy a generous leadership stipend leading the new OB/GYN Hospitalist team in a recently updated, state-of-the-art facility.

**Facility Medical Director**  
AdventHealth Ocala  
Receive a wonderful work-life balance with this employed leadership position with competitive pay plus full benefits package.

teamhealth.com/join  
865.408.7237

Olive View-UCLA Medical Center, a Los Angeles County facility and major teaching hospital for the David Geffen School of Medicine at UCLA, is recruiting a full-time BC/BE general obstetrician/gynecologist.

We are seeking individuals who will contribute to an academic, energetic and creative multidisciplinary faculty. Responsibilities include direct patient care with strong emphasis on mentoring and training residents in the UCLA Ob/Gyn Residency Program, as well as the teaching of medical students. Opportunities in clinical and health services research are available and encouraged. Employment includes an academic appointment at the David Geffen School of Medicine at UCLA. Competitive salary and benefits provided. Applicants at the level of Assistant or Associate Professor will be considered. This is an excellent opportunity in sunny Southern California for interested academicians. Applicant must be eligible for licensure in California. EOE

Please submit letter of intent, CV, and three references to: Dr. Christine Holschneider, Chair, Department of Obstetrics and Gynecology, Olive View-UCLA Medical Center, 14445 Olive View Drive, 6D-116, Sylmar, CA, 91342.  
Email: cholschneider@dhs.lacounty.gov

Faculty Positions in Obstetrics & Gynecology
The George Washington University Medical Faculty Associates Inc., an independent, non-profit clinical practice group affiliated with the George Washington University, is seeking to fill several full-time faculty generalist physician positions in the Department of Obstetrics and Gynecology. Non-tenure track appointments will be made at a rank (Instructor/Assistant Professor/Associate Professor/Professor) and salary commensurate with experience. These physicians will have clinical as well as teaching and administrative responsibilities.

The physician generalists will work 4-6 half-day sessions in the clinical area as well as on the labor and delivery unit, and will have two half-days to perform surgery and pursue administrative and scholarly projects. They will also have weekend and night call responsibilities in the labor and delivery unit.

**Basic Qualifications:** Applicants must be board certified in Obstetrics and Gynecology or on schedule for board certification and must be eligible for licensure in the District of Columbia and Maryland.

**Application Procedure:** To be considered, please complete an online application at [http://gwu.jobs/postings/71714](http://gwu.jobs/postings/71714) and upload a letter of interest and a CV. Review of applications will begin on February 18, 2020 and will continue until the positions are filled. Employment offers are contingent on the satisfactory outcome of a standard background screening. Only complete applications will be considered.

The George Washington University and the George Washington University Medical Faculty Associates are Equal Employment Opportunity/Affirmative Action employers that do not unlawfully discriminate in any programs or activities on the basis of race, color, religion, sex, national origin, age, disability, veteran status, sexual orientation, gender identity or expression, or on any other basis prohibited by applicable law.
Was this prolapse properly managed?
In a case with multiple defendants, coordinating defenses should be the primary objective for trial.

Facts
Before being treated by Defendant ob/gyn A, the plaintiff had seen Co-defendant ob/gyn B in January 2013 for worsening symptoms of prolapse. Her complaints included incomplete voiding, urinary frequency, nocturia, urgency two to four times per day, and some rare episodes of stress urinary incontinence (SUI).

Dr. B found that the plaintiff had evidence of Stage II uterovaginal prolapse 1 cm past the hymen. His impression was uterine prolapse, cystocele, rectocele, and urinary incontinence, and a need to rule out voiding dysfunction. The plaintiff’s treatment by Dr. B continued through the winter of 2013, during which various surgical interventions were explained to her. She ultimately gave him consent for a laparotomy, supracervical hysterectomy, bilateral salpingo-oophorectomy (BSO), sacrocolpopexy with permanent mesh, possible cystocele and rectocele repair, and cystoscopy.

The plaintiff underwent surgery with Dr. B at Codefendant Hospital on May 7, 2013. Dr. B discussed the risks of surgery with the plaintiff including possible bowel injury. He encountered significant scarring, which he stated might be secondary to previous obstetrical injury. He did not perform the sacrocolpopexy because of his intraoperative findings of a deep pelvis, pelvic adhesions, redundant bowel, and diverticular disease. In the setting of an obese woman with diabetes, risk of infection and mesh erosion was greater, therefore, he elected to perform a modified colpopexy.

The plaintiff was on disability from May through July 2013 and Dr. B continued to treat her during that period. However, by the August 19, 2013 visit with Dr. B, it appeared that the plaintiff was having recurrence of prolapse. He had a long conversation with her but did not recommend any surgical intervention. The plaintiff’s last visit with Dr. B was on November 18, 2013. He noted she was having recurrence of prolapse. He had a long conversation with her but did not recommend any surgical intervention. The plaintiff’s last visit with Dr. B was on November 18, 2013. He noted she was having chronic constipation, and was not only bothered by vaginal protrusion, but there were days when she felt some discomfort. On exam, Dr. B noted excellent healing of the abdominal incision and no apical approach or cystocele. During maximal straining, a small Stage I rectocele and distal component 2 cm above the hymen was noted. There were no foreign bodies in the vagina and no antrocele. Dr. B instructed the plaintiff to do pelvic floor exercises and to lose weight. He noted that at that time he was very pleased with the results.

On February 24, 2014, the plaintiff presented to Nonparty ob/gyn C and his facility for an assessment of her recurring vaginal prolapse. Dr. C noted that she was a 62-year-old G4P3 who presented with a chief complaint of occasional urgency with leakage. She also admitted to frequency and nocturia but denied urinary leakage with cough, laugh or sneeze (SUI). She reported feeling a bulge and was status post-supracervical abdominal hysterectomy, uterosacral ligament suspension, and posterior repair done in May 2013 at Co-defendant Hospital (by Dr. B). Dr. C indicated that he reviewed those records and that Dr. B had originally consented to doing the surgery.

FOR MORE LEGALLY SPEAKING
TURN TO PAGE 22

Andrew I Kaplan, Esq is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation. This case was handled by one of his partners.
IMVEXXY* (estradiol vaginal inserts)  
**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 5.6 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 dose 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 (5.2), 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. It is unknown whether 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.

**CONTRAINDICATIONS**

Bone and Joint Pain

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.

**TherapeuticsMD**

**REVISED: 04/2019**
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

DISCOVER A TREATMENT EXPERIENCE WITH SIMPLICITY AT ITS CORE

THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES

PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)

MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED

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:

IMVEXXY is a registered trademark of TherapeuticsMD, Inc. © 2019 TherapeuticsMD, Inc. All rights reserved. IVXY-20291 12/2019