Well woman
Preventative screening guidelines in the 21st century

Life-long care for the ob/gyn patient includes age-appropriate testing that goes beyond the pelvic exam, as reflected in the anatomy highlighted in our “Vitruvian woman.”
Help your patients understand both of their LARC location options

LARC = long-acting reversible contraceptive

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.

- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

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

- Rule out pregnancy before inserting NEXPLANON.

Educate her about the risk of serious vascular events

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

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NEXPLANON is the only non-uterine LARC option

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

Placed subdermally in the inner upper arm just under the skin

* NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.
† Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

SELECTED SAFETY INFORMATION (continued)

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information

Nexplanon

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSEAGE AND ADMINISTRATION

The effectiveness of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should instruct and train prior to performing insertion and/or removal of NEXPLANON.

A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the subcutaneous tissues. Deep insertions or infections may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesia, bleeding, hematoma, scarring or infection may occur.

NEXPLANON may be deeply (intramuscular or intracutaneous) inserted subdermally or intravascularly. In cases where the implant has migrated to the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, myositis or muscle necrosis may be seen. In such cases, surgery may be required for removal. If any time the implant cannot be palpated, it should be localised and removal is recommended.

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

3. Ectopic Pregnancies

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON. Benign or malignant tumors of the ovary may render the control of hyperlipidemia more difficult.

4. Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism).

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

1. Complications of Implantation and Removal

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

If NEXPLANON is deeply (intramuscular or intracutaneous) inserted subdermally or intravascularly, the implant should be removed. Incomplete insertions or infections may lead to expulsions. Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deep, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site which may be related to deep insertion. There also has been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the subcutaneous tissues, the implant may not be palpable and/or removed after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesia, bleeding, hematoma, scarring or infection may occur.

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

2. Changes in Menstrual Bleeding Patterns

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (abrupt, 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 (11 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding 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 patterns were the most common reason for stopping treatment (1.3%) and withdrawal (1.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3.315 intervals of 90 days reported by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding on a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

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

<table>
<thead>
<tr>
<th>Total Days of Spots or Bleeding</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Days 91-180 (N = 745)</td>
<td>Treatment Days 271-450 (N = 657)</td>
</tr>
<tr>
<td>0 Days</td>
<td>17%</td>
</tr>
<tr>
<td>1-7 Days</td>
<td>30%</td>
</tr>
<tr>
<td>8-21 Days</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;21 Days</td>
<td>35%</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>% of 90-day Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent</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 the implant insertion.

1% = Percentage of 90-day intervals with this pattern

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

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 may be considered. Women with hypertension using NEXPLANON should be closely followed. If 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.

11. Carbohydrate and Lipid Metabolic Effects

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

12. Depressed Mood

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

13. Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels of blood decreased but were not used by pregnancy by one week after the removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.
14. Fluid Retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients whose conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

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

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

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

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

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

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

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

<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>Weight Increase</td>
<td>2.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.6%</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.
| ‡Among US subjects (N = 330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-raqiapoe 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-raqiapoe Etonogestrel Implant (IMPLanon®)

<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>10.9%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.5%</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>9.6%</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>7.6%</td>
</tr>
<tr>
<td>Dysmenorrhea</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 3.2% of subjects. Additionally, hematomas (3.0%), bruising (2.0%), pain (1.1%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives
Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as ritonavir, efavirenz, fosamprenavir, atazanavir, lopinavir/ritonavir, or indinavir can increase the plasma concentrations of etonogestrel, including etonogestrel.

Substances decreasing the plasma concentrations of HCs: Some drugs or herbal products that decrease the plasma concentrations of progestins, including etonogestrel.

Peptide reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir]) HC protease inhibitors (increase [e.g., bupropion and tegafur] or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efavirenz] or increase [e.g., etravirine]). These changes may be clinically relevant in some cases. Consult the prescribing information of antiretroviral and anti-retroviral concomitant medications to identify potential interactions.

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

USE IN SPECIFIC POPULATIONS

1. Pregnancy
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant (see Contraindications). Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 761 times the anticipated human dose (60 µg/day) of NEXPLANON should be removed if maintaining a pregnancy.

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

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

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

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

6. Overweight Women
The effectiveness of the etonogestrel implant in women who weighed more than 10% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations and concentrations of etonogestrel were inversely related to the weight. NEXPLANON decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE
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 (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was non-genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.

• Counsel women about the insertion of NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a copy of the USER CARD and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.

• Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.

• Counsel women that NEXPLANON does not protect against HIV or other STDs.

• Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

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

For more detailed information, please read the Prescribing Information.

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Over the past year Contemporary OB/GYN has undertaken an intense examination of the common causes of the 700 maternal deaths that occur each year in the United States. I am very grateful for the extraordinary skill and dedication brought to this project by our series editor, Dr. Carolyn Zelop. This important topic has also attracted the attention of professional organizations, foundations, and state and federal governments. Why is this subject so difficult to wrap our arms around? Well, for a start, there are many definitions of maternal mortality (see Table) and no universally accepted approach taken by individual states to measure its occurrence. In fact, because of uneven state uptake of the 2003 national death certificate, the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics hasn’t published an official Maternal Mortality Ratio for the United States since 2007.

The Global Burden of Disease group, using a sophisticated statistical algorithm, reported that the US maternal mortality ratio (MMR) increased from 16.9 per 100,000 livebirths in 1990 to 26.4 per 100,000 livebirths in 2015. During that same period, the global MMR declined 30%. Among 31 nations in the Organization for Economic Cooperation and Development, the United States ranks 30th in maternal mortality with rates three times higher than Canada and the UK. However, at least 80% and perhaps all of this increase can be attributed to improved ascertainment among states implementing the updated death certificate format which contains a detailed set of pregnancy questions. While we can take some comfort in this epidemiological solace, none of us should be satisfied until every preventable maternal death is avoided. But this begs the question of exactly what percent of maternal deaths are preventable?

**Pregnancy-related deaths**

To answer that question, we need more detailed and accurate data. The CDC’s Pregnancy Mortality Surveillance System (PMSS) tracks both pregnancy-associated and pregnancy-related deaths (PRDs). The former is defined as any death of a woman during pregnancy or within the first postpartum year irrespective of whether the fatality is truly pregnancy-related. The latter includes all deaths of women during or within 1 year of pregnancy caused by a pregnancy complication or a chain of events initiated by pregnancy, or aggravation of an unrelated condition by physiologic effects of pregnancy. Thus, while all PRDs are pregnancy-associated, not all pregnancy-associated deaths are pregnancy-related.

Read more about Contemporary OB/GYN’s maternal mortality coverage on PAGE 27
Because it is ascertained using both birth and death certificate data abstracted and analyzed by medical epidemiologists, the PRD rate is a far more accurate estimate of true US maternal mortality than the MMR. The CDC reports that the US pregnancy-related mortality ratio has increased from 7.2 deaths per 100,000 live births in 1987 to 18.0 deaths per 100,000 live births in 2014, although, as with the MMR, much of this increase is related to enhanced ascertainment and possible over-estimation. Importantly PRDs are tracked and analyzed by state maternal mortality review committees (MMRCs) to determine the exact causes of and contributing factors to maternal deaths and to generate estimate of preventability.

The reports issued by those 35 states with MMRCs are extraordinary sources of detailed information on PRDs. Structured, detailed, and relevant data are collected using the CDC’s Maternal Mortality Review Information Application (MMRIA) from information gleaned from a variety of sources including birth and death certificates, newspaper stories, obituaries, and medical records. The MMRCs then opine as to the immediate causes of deaths, contributing factors and the percentage of deaths that are preventable.

Report from nine Maternal Mortality Review committees
This year, nine states (Colorado, Delaware, Georgia, Hawaii, Illinois, North Carolina, Ohio, South Carolina and Utah) reported on pooled PRD data developed through the CDC’s MMRIA and its predecessor, the Maternal Mortality Review Data System to describe lessons learned. Some of their findings will not come as a surprise to our readers. For example, half of all PRDs studied were caused by hemorrhage, cardiovascular and coronary conditions, cardiomyopathy, or infection. Nor should it be a surprise that significant racial disparities exist with non-Hispanic black women being three to four times more likely to suffer a PRD than non-Hispanic white women.

Web-based toolkits used by the California Maternal Quality Care Collaborative have helped decrease maternal mortality in the state by 57% from 16.0 to 7.3 deaths per 100,000 livebirths.

DEFINITIONS OF MATERNAL DEATH

- **Maternal mortality ratio** - maternal mortality ratio refers to number of maternal deaths during given time period per 100,000 live births.

- **Maternal mortality rate** - number of maternal deaths in given period per 100,000 women of reproductive age (15 to 49 years) during the same time period.

- **Maternal death** - death of a woman while pregnant or ≤ 42 days of termination of pregnancy, irrespective of duration and site of pregnancy, from any cause related to or aggravated by pregnancy or its management, but not from accidental or incidental causes (based on death certificates).

- **Late maternal death** - death of a woman from direct or indirect obstetrical causes > 42 days but < 1 year after termination of pregnancy.

- **Pregnancy-associated death** - death of a woman while pregnant or within 1 year of the termination of pregnancy, regardless of cause; includes pregnancy-associated but not related deaths (e.g., death of pregnant woman in an earthquake) and pregnancy-related deaths (see below).

- **Pregnancy-related death** - death of a woman while pregnant or within 1 year of the end of a pregnancy, regardless of the outcome, duration or site of the pregnancy from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. (based on birth and death certificates analyzed by medical epidemiologists)
The report indicates that the percentage of pregnancy-associated deaths that were pregnancy-related is 35% overall but that the PRD proportion of pregnancy-associated deaths increase with maternal age from 25.7% in women aged 25 to 29 years to 42.3% in women aged 35 to 44. Women in this older age group are more likely to die from cardiovascular disease, hemorrhage, and embolism than younger women while the latter are more likely to die of cardiomyopathy, infection, and mental health conditions. Non-Hispanic black women have a higher percent of pregnancy-associated deaths that were pregnancy-related (48.2%) than either non-Hispanic whites (28.4%) or Hispanic women (30.2%). While African-American women are nearly twice as likely to die from (pre)eclampsia and embolism, non-Hispanic white women were nearly 10 times more likely to have a PRD linked to mental health conditions.

Among women with PRDs, 38% occur during pregnancy, 45% within 42 days of a delivery or termination and 18% occur between 34 days and 1 year postpartum. Among PRDs occurring during pregnancy, hemorrhage and cardiovascular/coronary conditions each account for about 20% of deaths followed by embolism (9.2%) and mental health conditions (6.6%). The leading causes of PRDs within 42 days of birth/termination were infection (21.7%) followed by hemorrhage (12.4%), cardiovascular/coronary conditions (12.4%) and (pre)eclampsia (9.3%). Among PRDs occurring between 43 days to 1 year postpartum, cardiomyopathy (32.4%), mental health conditions (16.2%), and venous thromboembolism (VTE) (10.8%) were the most common causes.

The report notes that three primary factors—systems of care, provider factors, and patient factors—contribute to virtually all PRDs. For example, among deaths due to hemorrhage, deficient systems of care (e.g., inadequate training, unavailable personnel, absence of policies and procedures and lack of coordinated care) account for 36% of contributing factors. Provider factors such as missed or delayed diagnosis and ineffective treatment accounted for 31% of contributing factors while patient factors including a lack of knowledge of warning signs or failure to seek care accounted for 26% of contributing factors. The report concludes that addressing these factors would prevent 70% of hemorrhagic deaths. Overall, the authors estimate that 63.2% of PRDs could be prevented by addressing these and similar contributing factors. They further opine that 63.2% of PRDs occurring during pregnancy are potentially preventable while 66.7% of such deaths occurring within 42 days of birth/termination and 58.3% of deaths occurring between 43 days and 1 year postpartum are preventable.

**Interventions to prevent pregnancy-related deaths**

The repetitive themes emerging from the report form the basis of recommendations to reduce PRDs. The authors conclude that the greatest benefits would accrue public policies addressing the social determinants of care, which is obviously the most difficult strategy to implement. The next largest benefit would result from ensuring that patients receive the appropriate level of care for their condition—analogous to the regionalization of perinatal care in neonatal intensive care units.
Recommendations more readily under our control include improving:

- access to care and patient/provider communication
- patient management of mental health conditions
- communication and coordination of care among providers
- standards of assessment, diagnosis, and treatment
- language translation (medical literacy)
- prevention initiatives, including substance abuse screening, prevention, and treatment programs

That such approaches work has been demonstrated by the California Maternal Quality Care Collaborative. Since its founding in 2006, the collaborative has used web-based care toolkits to help decrease maternal mortality by 57% from 16.0 to 7.3 deaths per 100,000 livebirths. In 2017, 211 hospitals participated, covering 95% of deliveries. Nationally, the Alliance for Innovation on Maternal Health, (AIM) launched by the federal Health Resources Service Administration (HRSA) Maternal Child Health Bureau and led by the American College of Obstetricians and Gynecologists (ACOG) in collaboration with many other societies, seeks to reduce severe maternal morbidity and mortality using safety bundles. Currently more than 20 states and 800 hospitals participate.

In Washington, ACOG and other societies are supporting legislation designed to expand MMRCs to all 50 states. The Preventing Maternal Deaths Act of 2017, H.R.1318, and the Maternal Health Accountability Act of 2017, S.1112, would fund the Department of Health and Human Services (HHS) to make grants available to establish and coordinate a national MMRC network, accelerating the introduction of best practices. Happily, both have recently been passed by the House of Representatives and the Senate.

**Take-home message**

The United States has the dubious distinction of having among the highest rates of pregnancy-related deaths in the industrialized world. Even more distressing, we are the only such nation to have rising maternal mortality rates. The availability of MMRCs in every state along with the universal deployment of patient safety bundles such as those advocated by the AIM program are the surest and fastest approaches to reducing this national tragedy. Developing regionalized maternal care levels analogous to perinatal care levels would also likely reduce PRDs. Finally, because obesity is a major contributor to severe maternal morbidity and mortality from cardiac disease, VTE, depression, and (pre)eclampsia and confers many long-term adverse health sequelae, it should be a major focus of U.S. prevention efforts. While not all maternal deaths can be prevented by these actions, the opportunity to prevent nearly two-thirds of maternal deaths in this Nation must be seized upon.

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FOR REFERENCES VISIT contemporaryobgyn.net/PreventMaternalMortality
Opening the ob/gyn door for sexual and gender minority patients

Ob/gyns who are open, accepting and supportive of the SGM community can help eliminate critical health disparities and also reap benefits for their practices.

by ALEXIS LIGHT, MD, AND JUNO OBEDIN-MALIVER, MD, MPH, MAS

In 2011, the American College of Obstetricians and Gynecologists (ACOG) published Committee Opinion #512, “Health care for transgender individuals” and in 2012 it published Committee Opinion #525, “Health care for lesbians and bisexual women.” Years later, however, many ob/gyns are still grappling with how to fit into their clinical practices caring for sexual and gender minority (SGM) people, which include but are not limited to lesbian, gay, bisexual, transgender, and queer and questioning (LGBTQ) people.

According to a 2017 Gallup poll, the LGBTQ population represents at least 4.5% of the adult population (~11 million Americans). The percentage is higher among millennials at 7.3%, and increasing as a recent study found 27% of California youth are gender non-conforming. Therefore, it is imperative that we learn how to integrate care for SGM people into our practices. However, many studies show that doctors receive little training on LGBTQ health care and many ob/gyns lack critical knowledge about caring for LGBTQ people. We hope to support you by filling in gaps to meet this critical need.

Why focus on SGM people?
Due to long-standing discrimination and stigma, SGM people have health disparities and are less likely to get the health care they need. Numerous studies have shown that: SGM people are less likely to obtain needed preventative care.

Ob/gyns should recognize that sexual orientation, gender identity and sex assigned at birth are different components and should be considered as such.

The 3 principles of caring for SGM patients are: SGM people are different from cisgender/straight people, SGM people are the same as cisgender/straight people and SGM people are unique from one another.

Ob/gyns who are open, accepting and supportive of the SGM community can help eliminate critical health disparities and also reap benefits for their practices.
ment; face discrimination, stigma, neglect, and poor treatment in doctors’ offices; and have to teach their doctors how to take care of them. This is true throughout health care, including sexual and reproductive health care.6-11

**What do ob/gyns need to know to better care for SGM patients?**

First, who we are talking about? The term SGM is increasingly used including by the National Institutes of Health, replacing LGBTQ as a bigger, more inclusive umbrella term. SGM includes everyone who is not cisgender (i.e., their gender identity aligns with sex assigned at birth) and straight. Many people who might have been traditionally overlooked or excluded by “LGBTQ” fit under the SGM umbrella, including people who are asexual, pansexual, agender, genderqueer, gender non-binary, and two-spirit, to name an unexhaustive few.

The second fundamental piece is to appreciate that sexual orientation, gender identity (often abbreviated together as “SOGI”), and sex assigned at birth are different components of people’s lives and need to be considered separately.

**Sexual identity, sexual behavior, and attraction.** Sexual orientation comprises three different domains of every person’s experience: identity, sexual behavior, and romantic and/or emotional attraction. These three domains have distinct health correlates which research has shown may not all line up.12 One study noted that 25% of adult lesbian-identified women were having sex with (assumed cisgender) men,13 highlighting the difference between sexual orientation and sexual behavior and having obvious implications around pregnancy planning and contraception, among other considerations. Whereas sexual behaviors inform sexually transmitted infection (STI) risk screening or whether to proceed with a colposcopy for prolapse, considerations of sexual identity help clinicians understand social support networks, durable power of attorney/partner benefits, and legal documents needed before birth. Attraction also may be particularly relevant to discussions of sexual arousal dysfunction.

**Gender identity.** In contrast, gender identity is one’s internal sense of their gender and their sense of being a woman, man, or another gender, including non-binary gender identities. Although often tied to gender expression—how people present themselves with language, dress, hair, make-up, voice, or mannerism etc.—gender identity and gender expression are still distinct characteristics. You cannot know someone’s gender identity without asking them. However uncomfortable asking may seem, it is critical to understanding who people are and how they would like to be referred to. (See more on asking about gender identity below).

**Sex.** Another distinct category is someone’s sex, more specifically sex assigned at birth, which is a constellation of one’s physical anatomic, metabolic, and chromosomal make-up. Knowing an individual’s sex assigned at birth is critical to understanding the organs they were born with: informing preventative care management like relevant cancer screenings and other anatomically relevant pathologic risks. Sex assigned at birth is also important in appreciating and supporting reproductive and family planning goals, and how to assist someone with desired gender-affirming medical or surgical procedures.14 A note of caution: Sex assigned at birth is often assessed by examination of external genitalia. Experience of people with differences in sex development (formerly called disorders of sex development) such as androgen insensitivity syndrome (AIS) and for people who have had gender-affirming genital surgery (such as vaginoplasty) teach us that external genitalia may not correspond with internal organs or reproductive capacity.

**Putting it together.** Having discussed the difference between sexual orientation, gender identity, and sex assigned at birth, it is important to understand how these domains are both distinct and overlapping features of our patients’ experiences. These components are also coupled with other aspects of experience and identity such as someone’s age, race/ethnicity, education, socioeconomic status, religion, region, family structure, etc. In thinking about how all of these components interact, we start to appreciate the importance of one’s gender and sexual orientation in their health as part of the layers of complexity and beauty of SGM people’s lives.
So how to get started in patient care?

Dr. Obedin-Maliver has coined two different simple frameworks to educate other providers about caring for SGM patients: “The 3 principles” (Figure 1) and “The 4 doors” (Figure 2). Let us start by looking at “The 3 principles”:

**PRINCIPLE 1: SGM people are different from cisgender/straight people.**

It is important to note that SGM disproportionately experience health disparities and resiliencies that manifest in different risk factors and health outcomes. An example is that cisgender lesbian women and transgender men are less likely to be up-to-date on Pap smears and for transgender men, Pap smear insufficiency is higher than for cisgender women. Cancer rates may also be higher, but because cancer registries do not collect such information, we are limited in our understandings. Depression, anxiety, substance use, cardio-metabolic risk factor differences, self-reported health and well-being, obesity, diabetes, and asthma rates are all different between SGM and non-SGM people. Why is this? Well, according to the minority stress theory, living and moving in the world as a SGM person in a socio-cultural landscape that is designed for cisgender and straight people can be tough. This results in poor health. From infancy on, gender is assumed to be consistent with one’s sex assigned at birth and it is assumed that people of one sex will be attracted to those of the other (another) sex. You can see the heteronormative and cisnormative push everywhere once you start to look: consider baby onesies in the “boy’s” section stating “lady killer” or the gendered norms that say a young girl is a “tom boy” if she likes to be outside or play sports. Clearly this extends into adulthood with popular and very gendered magazines that focus on specific gender roles, including opposite-gender dating, romantic novels, wedding magazines, pregnancy and parenting books.

Findings and experiences of the SGM population who “break” societal assumptions might surprise you. We authored a study about the experiences of transgender men who experienced pregnancy after transitioning. In this initial study and follow-up interviews, we found that despite typical notions of womanhood and manhood, transgender men desired pregnancy. Though some had gender dysphoria in relation to having what is generally considered the sole purview of women, some saw pregnancy as a clear and unconflicted path to fatherhood. Here we have a glimpse into the lived reality of SGM people that is so often in conflict with normative expectations, services, and resources.

**PRINCIPLE 2: SGM people are the same as cisgender/straight people.**

Despite different experiences of moving through the world, fundamental medical principles, biology, and anatomy still apply to SGM people. Therefore, if someone has an organ, cancer screening should continue: the “if you have it, screen it” mantra applies. All the services that an ob/gyn and other reproductive and sexual health expert provides will be needed and should be made accessible to SGM people. These include but are not limited to: routine preventative gynecological care; treatment for pelvic, vulvar, and vaginal pathology; infertility treatment; full-spectrum family planning (including contraception, abortion, preconception, perinatal, postpartum care); breast/chest feeding support; cancer screening and treatment; and infectious disease screening and treatment. Each of these may need to be modified to be appropriate patient-centered care, but all of these services will be needed at some point by SGM people and should be framed to be comfortable and welcoming for people of any gender and sexual orientation.

**PRINCIPLE 3: SGM people are unique and different from one another.**

It would be laughable to assume that if you have seen one woman give birth or undergo a hysterectomy that you have seen them all. Similarly, SGM people are unique from one another. What one bisexual cisgender woman wants...
for support around sexual dysfunction may be very different than what another bisexual cisgender woman wants. To carry it further, because one transgender man wants a hysterectomy and bilateral salpingo-oophorectomy as part of his gender affirmation does not mean that all transgender men desire this, as has been shown by the United States Transgender Survey of over 27,000 participants. Work with your patients, be aware of some trends and considerations that can inform conversations, but don’t be prescriptive. Being SGM is one aspect of people’s lives, but it is not determinative, nor monolithic. As mentioned above, other aspects of people’s lives and identities, such as race, ethnicity, education, class, geography, native and preferred languages, partnership, religion, family structure, employment etc. are also critical to consider as they interact with care decisions, resources, and needed services.

Now using basic principles, the concept of the “4 Doors” helps clinicians think about how to create an accessible and safe clinical practice for SGM people (Figure 2).

**DOOR 1: What happens when you get in the door?**

Good patient care starts before a patient ever sees a health care provider. In a vulnerable time of getting health care, being respectfully treated and feeling welcome goes a long way to helping establish a good clinical rapport that can lead to a healing interaction. Some examples of this are ensuring that your registration process and front desk staff respectfully ask and consistently use people’s correct pronouns and can gracefully document that there may be a difference between someone’s current gender identity and sex assigned at birth, between someone’s affirmed gender and legal gender marker on identification, or that the primary insurance holder of a pregnant woman may be a patient’s lesbian partner. Having a physical environment that affirms the personhood of all patients is also important. This means signage that reflects that people of different genders need obstetric and gynecological care services, magazines that show different types of parents and partnership, and posters that show different families. And this also means having bathrooms that are for people of any gender.

**DOOR 2: What happens behind closed doors (i.e., between you and the patient)?**

Interactions with clinicians are central to care experiences. Much has been written about the importance of patient-centered care and that starts with knowing patients. As discussed previously, learning how to ask about people’s lives, including their sexual orientation, gender identity, and sex assigned at birth in sensitive ways will enhance a therapeutic rapport. We recommend incorporating the questions in Box 1 into your daily clinical practice with every patient.

There are many ways to incorporate these questions into your practice setting. Some ob/gyns may prefer to ask for this information on a pre-visit questionnaire whereas others may exclusively ask the questions in the clinical interview. However you approach it, do ask! These questions should not be shied away from and are critical to supporting accurate evidence-based medical care. In a study of four clinics with over 300 people of all identities, most people wanted to be asked about their sexual orientation and gender identity and very few failed to answer the question.

**DOOR 3: What happens between doors?**

Often patients will need to be referred to other providers. Other providers may not have implemented the steps you have, or hopefully will soon, to support SGM people in your practice. But our patients view people we refer them to as extensions of our relationship with them. If they have a bad experience with another provider, it may not only undermine therapeutic goals, but your relationship. Therefore, calling ahead, noting (with permission) SGM status to the referring provider and following up with your patients about their experiences can go a long way.

**DOOR 4: What happens to get people into the door (i.e., thinking about SGM people as a sought-out population to serve and get expertise in)?**

For many providers, supporting SGM people may not be only a necessary component of providing excellent care.
to a broad swath of population, but also a way to grow your practice. We advocate for thinking about engaging with the SGM population as sought-out recipients of the care you provide. While ensuring your environment is supportive once people arrive is critical, thinking about how to bring more SGM people into your clinical space and making it a destination of choice can open up a new population to your practice and expand available services for a medically underserved community. Concrete steps include having SGM people and relationship/family patterns in signage and advertisements, focusing advertisements on experiences unique to SGM people, such as providing gender-affirming hormones for transgender men, reciprocal in vitro fertilization or “co-maternity services” for sexual minority women, and post-vaginoplasty care services for transgender women.

Next steps
Some resources to delve deeper into concrete steps you can take to shape SGM-supportive care environments are available from The Fenway Institute (https://www.lgbthealtheducation.org) and the Diversity and Inclusion Initiative and associated monograph from the Association for American Medical Colleges (https://www.aamc.org/initiatives/diversity/lgthealthresources/). Multiple organizations exist to help advocate for the care of SGM minorities and many put out information resources and directories for SGM patients and their providers, including GLMA: Health Professionals Advancing LGBTQ Equality (www.glma.org), Project HEALTH’s Transline e-consultation service for questions about advancing transgender health (http://project-health.org/transline/), the Human Rights Campaign (HRC), and the World Professional Organization for Transgender Health (WPATH) (www.wpath.org).

An additional quick online video training with avatars from the University of California, San Francisco (UCSF) can help take you through how to assess gender identity and sex assigned at birth.27

Providing care that is open, accepting, supportive, and when needed, tailored to the SGM community is the bold action that is needed now to help eliminate critical health disparities. By increasing your awareness, expanding your knowledge base, and tweaking your already existing scope of practice, you can help make a big difference.

DISCLOSURES - Dr. Light reports no potential conflicts of interest with regard to this article.
- Dr. Obedin-Maliver is a consultant for Ibis Reproductive Health.

FOR REFERENCES VISIT contemporaryobgyn.net/SGMPatients

EXAMPLES OF QUESTIONS on gender, sex assigned at birth, sexual orientation, and sexual behavior.

- What is your preferred name? And what pronouns do you use?
- What is/are your current gender(s)? (Answer options: open text field response)
- What was your sex assigned at birth (for example on your original birth certificate)? (Answer options: female, male)
- What is/are your sexual orientation(s)? (Answer options: open text field response)
- Have you ever been diagnosed with a difference of sex development or an intersex condition? If yes, please specify.
- What are your family planning goals?
- Do you currently feel safe in your relationships?
- Have you been sexually active in the last year?
- What are the gender(s) of your sexual partners? (Answer options: open text field response)
- What is your preferred language for your body parts?
- Though this may be awkward, I’m going to ask you explicitly about certain sexual behaviors. This helps me understand how I can best support you.
- Do you ever have sex where someone else’s penis comes in contact with your vagina/vulva/frontal genital opening (use preferred language here)?
- Do you have any history of trauma or assault that may affect your experience talking about sensitive topics or having a physical exam performed?
- Are you currently satisfied with your sexuality and sexual practices?
- Do you have any questions or concerns about intimacy or your body?
MIFEPRISTONE AND MISOPROSTOL

Medical management of missed abortion

Adding mifepristone to an ob/gyn’s armamentarium isn’t as easy as writing a prescription but women need access to this drug for missed abortion.

by NANCY L. STANWOOD, MD, MPH, AND ABIGAIL S. CUTLER, MD

Early pregnancy loss (EPL)—including missed, incomplete and inevitable abortion—is a common clinical outcome, experienced by approximately 1 million women every year.1 Currently, management of EPL includes expectant, medical and surgical options. Previous literature demonstrated that misoprostol, a prostaglandin E1 analogue, is most effective in patients diagnosed with incomplete or inevitable abortion, and especially in those who present with symptoms such as cramping and bleeding.2 However many women are diagnosed with EPL by ultrasound, prior to onset of symptoms. Among women diagnosed with anembryonic gestation and embryonic or fetal demise, in which symptoms of EPL are less common, a single dose of misoprostol will effectively complete an abortion in only 81% to 88%, respectively. A second dose of misoprostol can increase the rate of expulsion3 but this delay in success is associated with increased costs to both patients and the healthcare system, including more office visits, ultrasound examinations, and patient anxiety. While medical management with misoprostol is an important alternative to observation or a surgical procedure, we’ve all had patients for whom medical management resulted in a prolonged and frustrating process during a sensitive time. Wouldn’t it be great if we had a medical option that resulted in a more expeditious and safer resolution of pregnancy loss?

New evidence for better medical management

In “Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss” (New England Journal of Medicine, June 2018), Schreiber et al presented results of a randomized clinical trial involving 300 women who were confirmed to have a nonviable intrauterine pregnancy by 12 weeks estimated gestational age (EGA).4 Given the known high efficacy of mife-

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**INDICATION**

- GARDASIL 9 is a vaccine indicated in females 9 through 45 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by human papillomavirus (HPV) Types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- GARDASIL 9 is indicated in males 9 through 45 years of age for the prevention of anal cancer caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care professional.
- GARDASIL 9 has not been demonstrated to provide protection against diseases from vaccine HPV types to which a person has previously been exposed through sexual activity.
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; or cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), or anal intraepithelial neoplasia (AIN).

**INDICATION (continued)**

- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58.
- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

**SELECT SAFETY INFORMATION**

- GARDASIL 9 is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant].
- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion.
- Safety and effectiveness of GARDASIL 9 have not been established in pregnant women.
- The most common (≥10%) local and systemic adverse reactions in females were injection-site pain, swelling, erythema, and headache. The most common (≥10%) local and systemic reactions in males were injection-site pain, swelling, and erythema.
- The duration of immunity of GARDASIL 9 has not been established.

**DOSAGE AND ADMINISTRATION**

- GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
  - For individuals 9 through 14 years of age, GARDASIL 9 can be administered using a 2-dose or 3-dose schedule. For the 2-dose schedule, the second dose should be administered 6–12 months after the first dose. If the second dose is administered less than 5 months after the first dose, a third dose should be given at least 4 months after the second dose. For the 3-dose schedule, GARDASIL 9 should be administered at 0, 2 months, and 6 months.
  - For individuals 15 through 45 years of age, GARDASIL 9 is administered using a 3-dose schedule at 0, 2 months, and 6 months.

Please read the adjacent Brief Summary of the Prescribing Information.
**WARNINGS AND PRECAUTIONS**

**Syncope:** Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

**Managing Allergic Reactions:** Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL 9.

**ADVERSE REACTIONS**

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

The safety of GARDASIL 9 was evaluated in seven clinical studies that included 15,703 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also included 7,278 individuals who received at least one dose of GARDASIL 9 as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination record card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL 9.

The individuals who were monitored using VRC-aided surveillance included 9,059 girls and women 16 through 26 years of age, 1,876 boys and men 16 through 26 years of age, and 5,212 girls and boys 9 through 15 years of age (4,348 girls and 1,777 boys) at enrollment. Those who received GARDASIL 9; and 7,078 girls and women 16 through 26 years of age and 302 girls 9 through 15 years of age at enrollment received GARDASIL 9. The race distribution of the integrated safety population for GARDASIL 9 was similar between girls and women 16 through 26 years of age (55% White; 25.2% Other Races or Multiracial; 14.1% Asian; 3.5% Black); girls and boys 9 through 15 years of age and 55% White; 25.2% Other Races or Multiracial; 13.5% Asian; 5.4% Black), and boys and men 16 through 26 years of age (52.1% White; 27.5% Other Races or Multiracial; 13.8% Asian; 3.7% Black). The safety data of GARDASIL 9 was compared directly to the safety of GARDASIL in two studies (Study 1 and Study 3) for which the overall race distribution of the GARDASIL cohorts (67.0% White; 25.3% Other Races or Multiracial; 13.5% Asian; 3.6% Black) was similar to that of GARDASIL 9 cohorts. Safety of GARDASIL 9 in individuals 27 through 45 years of age is inferred from the safety data of GARDASIL 9 in individuals 9 through 45 years of age and GARDASIL 9 in individuals 9 through 45 years of age.

**Injection-Site and Systemic Adverse Reactions:** Injection-site reactions (pain, swelling, and erythema) were solicited using VRC-aided surveillance for five days after each injection of GARDASIL 9 during the clinical studies. The rates and severity of these solicited adverse reactions that occurred within five days following each dose of GARDASIL 9 compared with GARDASIL 9 in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL 9. Recipients of GARDASIL 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL 9.

**Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)**

<table>
<thead>
<tr>
<th>GARDASIL 9</th>
<th>Post any dose</th>
<th>Post any dose</th>
<th>Post any dose</th>
<th>Post any dose</th>
<th>Post any dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls and Women 16 through 26 Years of Age</td>
<td>7069</td>
<td>6997</td>
<td>6909</td>
<td>7071</td>
<td>6976</td>
</tr>
<tr>
<td>Injection-Site Adverse Reactions</td>
<td>6955</td>
<td>6913</td>
<td>6743</td>
<td>7022</td>
<td>6934</td>
</tr>
<tr>
<td>Pain, Any</td>
<td>70.7</td>
<td>73.5</td>
<td>71.6</td>
<td>88.9</td>
<td>58.2</td>
</tr>
<tr>
<td>Pain, Severe</td>
<td>0.7</td>
<td>1.7</td>
<td>2.6</td>
<td>4.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Swelling, Any</td>
<td>12.5</td>
<td>23.3</td>
<td>28.3</td>
<td>40.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Swelling, Severe</td>
<td>0.6</td>
<td>1.5</td>
<td>2.5</td>
<td>3.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Erythema, Any</td>
<td>10.6</td>
<td>18.0</td>
<td>22.6</td>
<td>34.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Erythema, Severe</td>
<td>0.2</td>
<td>0.5</td>
<td>1.1</td>
<td>1.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Systemic Adverse Reactions**

| Temperature ≥100°F | 1.7 | 2.6 | 2.7 | 6.0 | 1.7 | 2.4 | 2.5 | 5.9 |
| Temperature ≥38°C | 0.3 | 0.3 | 0.4 | 1.0 | 0.2 | 0.3 | 0.3 | 0.8 |

**Girls 9 through 15 Years of Age**

| Injection-Site Adverse Reactions | 290 | 297 | 296 | 299 | 299 | 298 | 299 |
| Pain, Any | 71.7 | 71.0 | 74.3 | 89.3 | 66.2 | 66.2 | 69.4 | 88.3 |
| Pain, Severe | 0.7 | 2.0 | 3.0 | 5.7 | 0.7 | 1.3 | 1.7 | 3.3 |
| Swelling, Any | 14.0 | 23.9 | 36.1 | 47.8 | 10.4 | 17.7 | 25.2 | 36.0 |
| Swelling, Severe | 0.3 | 2.4 | 3.7 | 6.0 | 0.7 | 2.7 | 4.1 | 6.3 |
| Erythema, Any | 7.0 | 15.5 | 21.3 | 34.1 | 8.7 | 14.4 | 18.4 | 29.8 |
| Erythema, Severe | 0 | 0.3 | 1.4 | 1.7 | 0 | 0 | 1.2 | 1.0 |

**CONTRAINDICATIONS**

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL 9.
## Table 1 (continued)

<table>
<thead>
<tr>
<th>Systemic Adverse Reactions</th>
<th>GARDASIL® 9 (N=200)</th>
<th>GARDASIL® 9 (N=229)</th>
<th>GARDASIL® 9 (N=299)</th>
<th>GARDASIL® 9 (N=291)</th>
<th>GARDASIL® 9 (N=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ≥100°F</td>
<td>2.3</td>
<td>1.7</td>
<td>3.0</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Temperature ≥102°F</td>
<td>0.3</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

The data for girls and women 18 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 16 years of age are from Study 3 (NCT01304498). N=number of subjects vaccinated with safety follow-up. n=number of subjects with temperature data. Pain, Anyn-withdrawal, moderate, severe, or unknown intensity. Pain, Severe:incapacitating with ability to work or do usual activity. Swelling, Any-to-severe size and/or unknown. Swelling, Severe:maximum size greater than 2 inches. Enzyma, Any-to-severe size and/or unknown. Enzyma, Severe:maximum size greater than 2 inches.

Unsolicited injection-site and systemic adverse reactions assessed as vaccine-related by the investigator were reported among recipients of either GARDASIL® 9 or GARDASIL® in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL® 9 = 0.1% vs. GARDASIL® <0.1%).

Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among ≥1.0% of Individuals after Any Vaccination with GARDASIL® 9 Compared with GARDASIL® (Studies 1 and 3)

<table>
<thead>
<tr>
<th></th>
<th>Girls and Women 16 through 26 Years of Age</th>
<th>Girls and Women 18 through 26 Years of Age</th>
<th>Girls and Women 18 through 26 Years of Age</th>
<th>Girls and Women 18 through 26 Years of Age</th>
<th>Girls and Women 18 through 26 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GARDASIL® 9 (N=7071)</td>
<td>GARDASIL® 9 (N=7078)</td>
<td>GARDASIL® 9 (N=299)</td>
<td>GARDASIL® 9 (N=291)</td>
<td>GARDASIL® 9 (N=294)</td>
</tr>
<tr>
<td>Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)</td>
<td>Pruritus</td>
<td>5.6</td>
<td>4.0</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
<td>1.9</td>
<td>1.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Hematoma</td>
<td>0.5</td>
<td>0.6</td>
<td>3.7</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Mass</td>
<td>1.3</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>1.0</td>
<td>0.7</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Induration</td>
<td>0.8</td>
<td>0.2</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Warmth</td>
<td>0.8</td>
<td>0.5</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Reaction</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)

|                  | Headache | 14.6 | 13.7 | 11.4 | 11.3 |
|                   | Pyrexia | 5.0 | 4.2 | 5.0 | 2.7 |
|                   | Nausea | 4.4 | 3.7 | 3.0 | 3.7 |
|                   | Dizziness | 3.2 | 2.8 | 0.7 | 0.7 |
|                   | Fatigue | 2.3 | 2.1 | 0.0 | 0.0 |
|                   | Diarrhea | 1.2 | 1.0 | 0.0 | 0.0 |
|                   | Orphanaged pain | 1.0 | 0.6 | 2.7 | 0.7 |
|                   | Malaise | 1.2 | 0.7 | 0.7 | 0.7 |
|                   | Aid-related pain | 0.7 | 0.8 | 1.7 | 1.3 |
|                   | Upper respiratory tract infection | 0.1 | 0.1 | 0.3 | 1.0 |

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498). N=number of subjects vaccinated with safety follow-up. In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL® 9 were similar between boys and girls. Rates of solicited and unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3. In another uncontrolled clinical trial with 1,234 boys and men and 1,075 girls and women 16 through 28 years of age (Study 7), the rates of solicited and unsolicited adverse reactions following each dose of GARDASIL® 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of solicited and unsolicited adverse reactions reported by boys and men 16 through 26 years of age in this study are shown in Table 3.

Table 3: Rates (%) of Solicited and Unsolicited® Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 Years of Age Who Received GARDASIL® 9 (Studies 2 and 7)

<table>
<thead>
<tr>
<th></th>
<th>Boys and Men 16 through 26 Years of Age</th>
<th>N=1394</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</td>
<td>Injection-Site Pain, Any</td>
<td>63.4</td>
</tr>
<tr>
<td></td>
<td>Injection-Site Pain, Severe</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Injection-Site Enthema, Any</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td>Injection-Site Enthema, Severe</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Injection-Site Swelling, Any</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>Injection-Site Swelling, Severe</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Oral Temperature ≥100.0°F</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Oral Temperature ≥102°F</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The data for GARDASIL® 9 boys 9 through 15 years of age are from Study 2 (NCT00543543). The data for GARDASIL® 9 boys 9 through 15 years of age are from Study 7 (NCT01619498). Unsolicited injection-site and systemic adverse reactions reported by ≥1.0% of individuals N=number of subjects vaccinated with safety follow-up. For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N=639, for boys and men 16 through 26 years of age N=1,386. Pain, Any-withdrawal, moderate, severe, or unknown intensity. Pain, Severe:incapacitating with ability to work or do usual activity. Swelling, Any-to-severe size and/or unknown. Swelling, Severe:maximum size greater than 2 inches. Enzyma, Any-to-severe size and/or unknown. Enzyma, Severe:maximum size greater than 2 inches. Serious Adverse Events in Clinical Studies. Serious adverse events were collected throughout the entire study period (range one month to 48 months past dose) for the seven clinical studies for GARDASIL® 9. Out of the 15,705 individuals who were administered GARDASIL® 9 and had safety follow-up, 356 reported a serious adverse event, representing 2.3% of the population. As a companion of the 7,378 individuals who were administered GARDASIL® 9 and had safety follow-up, 18% reported a serious adverse event, representing 2.5% of the population. For GARDASIL® 9, recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergic to vaccine, asthmatic crisis, and headache.

Deaths in the Entire Study Population: Across the clinical studies, ten deaths occurred (five each in the GARDASIL® 9 and GARDASIL® groups); none were assessed as vaccine-related. Causes of death in the GARDASIL® 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypovolemic septic shock, and one unexplained sudden death 6/8 days following the last dose of GARDASIL® 9. Causes of death in the GARDASIL® control group included one automobile accident, one airplane crash, one cerebral hemorrhage, one gunshot wound, and one stomach adenocarcinoma.

Systemic Autoimmune Disorders: In all of the clinical trials with GARDASIL® 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of GARDASIL® 9 recipients and 3.3% (240/7,378) of GARDASIL® 9 recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL® 9. AAHS control, or saline placebo in historical clinical trials.

Clinical Trials Experience for GARDASIL® 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL® A clinical study (Study 4) evaluated the safety of GARDASIL® 9 among 12- through 18-year-old girls and women who had previously been vaccinated with three doses of GARDASIL® 9. The first injection of GARDASIL® 9 ranged from approximately 12 to 36 months. Individuals were admistered GARDASIL® 9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL® 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL® 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL® 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL® 9 at a frequency of at least 1.2%, that occurred at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall the safety profile was similar between individuals vaccinated.
with GARDASIL® 9 who were previously vaccinated with GARDASIL® and those who were naïve to GARDASIL® vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL® (Tables 1 and 4).

### Table 4: Rates (%) of Solicited and Unsolicited Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL®

<table>
<thead>
<tr>
<th></th>
<th>GARDASIL® 9 N=608</th>
<th>Saline Placebo N=305</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-Site Pain</td>
<td>90.3 %</td>
<td>38.0 %</td>
</tr>
<tr>
<td>Injection-Site Lymphadenopathy</td>
<td>42.3 %</td>
<td>8.5 %</td>
</tr>
<tr>
<td>Injection-Site Swelling</td>
<td>49.0 %</td>
<td>5.9 %</td>
</tr>
<tr>
<td>Oral Temperature ≥38°C</td>
<td>6.5 %</td>
<td>3.0 %</td>
</tr>
<tr>
<td><strong>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-Site Pruritus</td>
<td>7.7 %</td>
<td>1.3 %</td>
</tr>
<tr>
<td>Injection-Site Hematoma</td>
<td>4.8 %</td>
<td>2.3 %</td>
</tr>
<tr>
<td>Injection-Site Reaction</td>
<td>1.3 %</td>
<td>0.3 %</td>
</tr>
<tr>
<td>Injection-Site Mass</td>
<td>1.2 %</td>
<td>0.7 %</td>
</tr>
<tr>
<td><strong>Unsolicited Systemic Adverse Reactions (1-14 Days Post-Vaccination, Any Dose)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19.6 %</td>
<td>18.0 %</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5.1 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.9 %</td>
<td>2.0 %</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3.0 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Abdominal pain, lower</td>
<td>1.5 %</td>
<td>0.7 %</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.2 %</td>
<td>1.0 %</td>
</tr>
</tbody>
</table>

*The data for GARDASIL® 9 and saline placebo are from Study 4 (NCT01047345).*

*Solicited adverse reactions reported by ≥1% of individuals.

N=number of subjects vaccinated with safety follow-up

For oral temperature: number of subjects with temperature data GARDASIL® 9 N=604; Saline Placebo N=303.

Safety in Comorbid Use with Menactra and Act pled: In Study 5, the safety of GARDASIL® 9 when administered concomitantly with Menactra (Meningococcal Groups A, C, Y and W-135) polysaccharide Diphtheria Toxoid Conjugate Vaccine) and Act HAV (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed [Tdap]) was evaluated in a randomized study of 1,241 boys (N=620) and girls (N=621) with a mean age of 12.2 years. Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection-site adverse reactions. The rates of injection-site adverse reactions were similar between the concomitant group and nonconcomitant group (vaccination with GARDASIL® 9 separated from vaccination with Menactra and Act HAV by 1 month) with the exception of an increased rate of swelling reported at the injection site for GARDASIL® 9 in the concomitant group (1.4%) compared to the nonconcomitant group (0.4%). The majority of injection-site swelling adverse reactions were reported as being mild to moderate in intensity.

Post-Marketing Experience: There is limited post-marketing experience following administration of GARDASIL® 9. However, the post-marketing safety experience with GARDASIL® 9 is relevant to GARDASIL® 9 since the vaccines are manufactured similarly and contain the same antigens from HPV types 6, 11, 16, and 18. Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure. The following adverse events have been spontaneously reported during post-approval use of GARDASIL® 9, and may also be seen in post-marketing experience with GARDASIL® 9. Blood and lymphatic system disorders: Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphopenopa thy, Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, Gastrointestinal disorders: Nausea, pancreatitis, vomiting, General disorders and administration site conditions: Asthenia, chills, death, fatigue, malaise, Immune system disorders: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria, Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis, Infections and infestations: Cellulitis, Vascular disorders: Deep venous thrombosis.

### Drug Interactions

Use with Systemic Immunosuppressive Medications: Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids used in greater than physiologic doses, may reduce the immune responses to vaccines.

### Use in Specific Populations

**Pregnancy:** Pregnancy Exposure Registry

There is a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to GARDASIL® 9 during pregnancy. To enroll in or obtain information about the registry, call Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-800-986-8999.

**Risk Summary:**

All pregnant women are at risk for birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of GARDASIL® 9 in pregnant women. Available human data do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when GARDASIL® 9 is administered during pregnancy.

In one developmental toxicity study, 0.5 ml of a vaccine formulation containing between 1 and 1.5-fold of each of the 9 HPV antigen types was administered to female rats prior to mating and during gestation. In another study, animals were administered a single human dose (0.5 ml) of GARDASIL® 9 prior to mating, during gestation and during lactation. These animal studies revealed no evidence of harm to the fetus due to GARDASIL® 9.

**Human Data:**

In pre-licensure clinical studies of GARDASIL® 9, women underwent pregnancy testing immediately prior to administration of each dose of GARDASIL® 9 or control vaccine (GARDASIL). [Data from GARDASIL® 9 are relevant to GARDASIL because both vaccines are manufactured using the same process and have overlapping compositions.] Subjects who were determined to be pregnant were instructed to defer vaccination until the end of their pregnancy. Despite this pregnancy screening regimen, some subjects were vaccinated very early in pregnancy before human chorionic gonadotropin (HCG) was detectable. An analysis was conducted to evaluate pregnancy outcomes for pregnancies with onset within 29 days before or after vaccination with GARDASIL® 9 or GARDASIL®. Among these pregnancies, there were 62 and 59 with known outcomes (excluding elective terminations and elective terminations) for GARDASIL® 9 and GARDASIL® respectively, including 44 and 48 live births, respectively. The rates of pregnancies that resulted in a miscarriage were 27.4% (17/62) and 12.7% (7/56) in subjects who received GARDASIL® 9, respectively. The rates of live births with major birth defects were 0% (0/44) and 2.1% (1/48) in subjects who received GARDASIL® 9, respectively.

A five-year pregnancy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL® 9 within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 2,586 of whom were prospectively followed. After excluding elective terminations (N=17), elective terminations (N=170) and those lost to follow-up (N=914), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates.

In two post-marketing studies of GARDASIL® 9 (one conducted in the U.S. and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL® 9 during pregnancy were evaluated retrospectively. Among the 1,740 pregnancies included in the U.S. study database, outcomes were available to assess the rates of major birth defects and miscarriage. Among the 498 pregnancies included in the Nordic study database, outcomes were available to assess the rates of major birth defects. In both studies, rates of assessed outcomes did not suggest an increased risk with the administration of GARDASIL® during pregnancy.

**Animal Data:**

Developmental toxicity studies were conducted in female rats. In one study, animals were administered 0.5 ml of a vaccine formulation containing between 1 and 1.5-fold of each of the 9 HPV antigen types 5 and 2 weeks prior to mating, and on gestation day 6. In a second study, animals were administered a single human dose (0.5 ml) of GARDASIL® 9 and 5 and 2 weeks prior to mating; on gestation day 6, and on lactation day 7. No adverse effects on pre- and post-weaning development were observed. There were no vaccine-related fetal malformations or variations.

**Lactation:** Risk Summary: Available data are not sufficient to assess the effects of GARDASIL® 9 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for GARDASIL® 9 and any potential adverse effects on the breastfed child from GARDASIL® 9 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

**Pediatric Use:** Safety and effectiveness have not been established in pediatric patients below 9 years of age.

**Geriatric Use:** The safety and effectiveness of GARDASIL® 9 have not been evaluated in a geriatric population defined as individuals aged 65 years and over.

**Immunocompromised Individuals:** The immunologic response to GARDASIL® 9 may be diminished in immunocompromised individuals.

For more detailed information, please read the Prescribing Information.

uspa-95314-181000

Sources: Merck

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VACC-1269505-DD00 10/18
MIFEPRISTONE AND MISOPROSTOL

FIGURE 1 THREE EASY STEPS TO PROVIDING MIFEPRISTONE

2. ORDER: Once registered, you may order the medication to be stocked in your office.
3. PATIENT ENCOUNTER:
   c. Have the patient take the medication in your office.

The Patient Agreement and Medication Guide are:
- Written specifically for the purpose of induced abortion care but still required when used for evidence-based off-label care, including early pregnancy loss.

As noted by that journal in June, the results were unequivocally in favor of pretreatment with mifepristone: 84% of patients in the mifepristone pretreatment group had treatment success compared to only 67% of women given misoprostol only. The number needed to treat (NNT) was six—low by any standard. Mifepristone pretreatment also reduced the need for additional surgical intervention: by 30 days, 24% of women in the misoprostol-alone group underwent surgical treatment compared to only 9% of women in the pretreatment group. In other words, women who did not receive mifepristone had a 3-fold risk of needing additional surgical intervention via uterine aspiration.

Importantly, complications were rare in both groups. Among women in the pretreatment group, 2% required blood transfusion and 1.3% were diagnosed with a pelvic infection – rates similarly infrequent among women who received only misoprostol, as well as among those who underwent surgical management. Side effects reported by women in both arms were also similar, although vomiting was more common among those who received pretreatment with mifepristone (27% versus 15%, P = 0.01). Thanks to Schrieber et al, we can now confidently conclude that pretreatment with mifepristone prior to administration of vaginal misoprostol is safe and superior to treatment with vaginal misoprostol alone. This regimen is the new standard of care for women who choose medical management of missed abortion.

**Incorporating the evidence into your practice**

For ob/gyns who are not familiar with mifepristone, making it available to patients requires more than simply writing a prescription. At the time of its approval in 2000, significant restrictions were placed on mifepristone’s availability—restrictions that, 18 years later, our best science does not support.

Mifepristone is regulated by the US Food and Drug Administration (FDA) with Risk Evaluation and Mitigation Strategy (REMS) and Elements to Assure Safe Use (EASU) requirements in order to be prescribed and dispensed. Regulations such as REMS and EASU are intended to apply to drugs that have been shown to cause serious adverse effects, such as antipsychotic medications that may lead to severe neutropenia and even death. Such restrictions are not intended to apply to low-risk drugs, such as erectile dysfunction medications, which are associated with death in only 0.004% of users.

Why then would mifepristone – with a mortality rate of six times less than Viagra5 – require a REMS restriction?
Patients who need mifepristone must find a clinician who stocks it in the office.

Strangely, mifepristone has never been shown to pose risks warranting REMS. This was evidenced recently by the FDA, which in 2016 approved an updated label for the drug that, among other things, removed language that the prescribed must be a physician and eliminated the requirement to report nonfatal adverse events. And yet, this requirement prevents prescription sales in retail pharmacies. In other words, patients who need mifepristone—for any indication or reason, be it a medical abortion, medical management of EPL or uterine fibroids—must find a clinician who stocks mifepristone in the office.

This is not an easy task. According to Danco, the manufacturer of Mifeprex, only 7% of sales nationwide were to private medical practices.7 Reluctance to stock the drug is thought to be widespread and reasons may include concerns about ordering, managing and dispensing a drug; costs (both of drug as well as related to wasted doses due to expiration prior to use); the burden of excessive paperwork; and, of course, stigma associated with use of mifepristone for induced medical abortion. All these factors jeopardize women’s access to our profession’s evidence-based standards of care.

Now we have yet another reason to make mifepristone more accessible to our patients. For ob/gyns who are seeking concrete steps to incorporate this new evidence into practice, please refer to Figure 1 and to www.contemporaryobgyn.net/MissedAbortion for access to the required forms.

### Some additional tips for success:

- **DON’T FORGET CONTRACEPTION COUNSELING!** According to recent research by Flink-Bochacki et al., women who experience spontaneous miscarriage are receptive to the idea of contraceptive counseling, but providers are inconsistent about offering it.8 For patients choosing medical management of EPL who desire immediate contraception (and especially for whom follow-up is challenging), consider starting contraception—be it pills, Depo Provera or Nexplanon—at the time of mifepristone initiation.

- **WRITE FOR AN ANTIEMETIC!** Authors noted an increased risk of nausea among women who received pretreatment with mifepristone. Consider providing a prescription for an antiemetic at time of treatment initiation.

### A call to action

Studies of use of mifepristone for both induced abortion and medical treatment of EPL have not demonstrated risks that support REMS regulation. In addition, recent research by Raifman et al. indicates that in countries where pharmacies have been allowed to dispense mifepristone, women enjoy increased access to evidence-based medical care without increased risks to their health.9,10 Indeed, our colleagues at the American College of Obstetricians and Gynecologists (ACOG) have advocated for removing the REMS restrictions from mifepristone provision for years.11-13

Put bluntly, we must not let abortion stigma prevent women from having access to the most effective therapy for a reproductive life event as common as miscarriage. Let’s join our colleagues at ACOG in exerting pressure on the FDA to remove a requirement that impedes our ability to provide safe, timely, evidence-based care. To make your voice heard, consider contacting the FDA yourself using their Health Professionals webpage (https://www.fda.gov/forHealthProfessionals/default.htm). Our patients deserve access to the new gold standard in reproductive health care, not restrictions that harm them.

### DISCLOSURE

The authors report no potential conflicts of interest with regard to this article.

### FOR REFERENCES VISIT

contemporaryobgyn.net/MissedAbortion

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We want to hear from you. Have you pretreated early pregnancy loss patients with mifepristone? How was your patient’s experience with using it? Are you a physician who stocks mifepristone in your office? Let us know what you think of this article by emailing us at COGeditorial@ubm.com.
Key points for today’s ‘well-woman’ exam
A guide for ob/gyns

In this interview, editor-in-chief Charles J. Lockwood reviews key changes in guidelines for preventive screening throughout a woman’s lifespan with experts in internal medicine and ob/gyn.

Pap smears and the annual exam

**DR LOCKWOOD:** It’s been a few years since I’ve seen routine annual exams when everyone received a Pap smear. What are the current guidelines for Pap smear screening and why the change?

**EMILY HALY, MD:** The US Preventive Services Task Force (USPSTF) did an analysis focusing on what frequency had the greatest value for screening. More screening doesn’t necessarily improve outcomes but does contribute to the higher cost of care.

**CATHY LYNCH, MD:** And as you know, especially younger women increases risk of procedures like cone biopsies that could lead to subsequent complications in pregnancy. Younger women are much more likely to clear human papilloma virus (HPV) infection, so frequent screening can result in intervention when the body was already working on clearing the infection.

**DR HALY:** The current recommendations from the USPSTF and the American Society for Colposcopy and Cervical Pathology (ASCCP) are for cytology screening from ages 21 to 29 every 3 years. From 30 to 64 years, screening can be cytologic every 3 years or cytology with high-risk HPV (HRHPV) testing every 5 years (co-testing). In women who have had negative screening Pap smear, testing can be discontinued at age 65. HPV testing is not recommended for women under age 21.

**DR LYNCH:** Keep in mind that a woman under 21 may still need testing for sexually transmitted disease (STD) but that does not include a Pap smear. Women who have had a hysterectomy performed for indications other than severe cervical dysplasia or cervical cancer no longer need Pap smear screening. Although HPV testing is not indicated as a screen in the 21- to 29-year group, it can be performed as a reflex test for management of atypical squamous cells of undetermined significance (ASCUS).
**DR LOCKWOOD:** Are the recommendations any different for women who have received the Gardasil vaccine?

**DR HALY:** Women who have had the HPV vaccine still follow the same Pap smear screening guidelines. Of all the vaccines I recommend, I find this one to be unique in that it is the first vaccine that can actually prevent cancer. Although there have been three different HPV vaccines, with development of the 9-valent Gardasil 9, it has become the only HPV vaccine available today. With coverage against HPV types 16, 18, 31, 33, 45, 52, and 58, Gardasil 9 provides prevention against cervical, vaginal, vulvar, anal, penile, and throat cancers. Because the vaccine also covers HPV types 6 and 11, it affords protection against the majority of HPV types associated with genital warts.

**DR LYNCH:** I recently had a mom ask me about the vaccine for her children that I had delivered. Her daughter is 14 and her son is 17. She said that she had been discussing the vaccine with them but they don’t like shots and they were not sexually active so she felt that they could delay getting the vaccine. I pointed out to her that since they didn’t like shots, it was to her daughter’s advantage to get the shot now when she would only need two shots versus waiting until 15 when she would then need three like her brother.

**DR HALY:** That’s a good point, between ages 9 and 14, only two shots are necessary to get immunity whereas for those ages 15 to 45, three shots are needed. The US Food and Drug Administration increased the age to 45 to help prevent HPV-associated diseases. The recommended time to administer Gardasil 9 to boys and girls is ages 9 to 14. That is because younger children respond with a higher immunologic response to the vaccine.

**Testing for infectious diseases**

**DR LOCKWOOD:** Have the guidelines changed for HIV testing?

**DR HALY:** The Centers for Disease Control and Prevention recommends testing all patients aged 13 to 64 for HIV. If prevalence of HIV is less than 0.1% then screening is not recommended. Patients can opt out of testing. In addition, you do not need their written consent to test for HIV. All pregnant women, patients initiating treatment for tuberculosis and those seeking treatment for STDs should be screened. HIV testing should be performed yearly on high-risk patients, including injection-drug users (IDU) and their sex partners, individuals who exchange sex for money or drugs, sex partners of HIV-infected individuals, and men who have sex with men (MSM) or heterosexuals who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.

**DR LYNCH:** In addition, STD testing should include yearly testing for chlamydia and gonorrhea in sexually active females under 25, and in those who are older if they have a new partner, multiple partners or a partner with a STD. Patients should be restested in 3 months after treatment for chlamydia or gonorrhea. Type-specific herpes simplex virus testing should be considered in patients who present for STD evaluation.

**DR LOCKWOOD:** Should I be testing for hepatitis C?

**DR HALY:** Hepatitis C testing should be done on women born between 1945 and 1965 and patients who are at high risk, including individuals born in regions of high endemicity (≥ 2% prevalence), IDU, MSM, individuals on immunosuppressive therapy, hemodialysis patients, and HIV-positive individuals.

**Screening for colorectal cancer**

**DR LOCKWOOD:** I have heard that colonoscopy screening guidelines have changed. Is that true and if so, why?

**DR HALY:** The American Cancer Society (ACS) has recently updated its colorectal cancer (CRC) screening guidelines to recommend screening average-risk patients for that disease at age 45. This recommendation changed based on an analysis (not a clinical trial) by ACS researchers showing that newer cases of colon cancers are occurring in younger patients.

**DR LYNCH:** Other organizations are sticking with their 50-year-old threshold recommendation for average-risk patients. The most important thing is to get people screened. There are now different options, including colonoscopy every 10 years, computed tomographic colonography (CTC) every 5 years, sigmoidoscopy every 5 years, take-home high-sensitivity guaiac-based fecal occult blood testing yearly, take-home fecal im-
munochemical testing (FIT) yearly, and multitetargeted stool-DNA testing every 3 years. If a non-colonoscopy test is positive, then a colonoscopy should be done.

**DR LOCKWOOD:** Have the guidelines changed for high-risk patients for CRC screening?

**DR HALY:** No. The guidelines still recommend screening at age 40 years or 10 years prior to age of diagnosis in a family member. Patients don’t want to have a colonoscopy because it is invasive and can be expensive, but it is the gold standard test. However, getting at least one of the tests that Dr. Lynch mentioned is better than none at all.

**Breast cancer screening**

**DR LOCKWOOD:** Can we talk about the different recommendations for breast cancer screening?

**DR LYNCH:** The controversy arises due to false-positive results at younger ages, which lead to unnecessary anxiety and further testing. Mammograms in younger women tend to be less accurate. Plus, there are no data to support that yearly screening in women less than 50 actually saves lives. All organizations recommend beginning screening in average-risk women no later than age 50 with the frequency varying from 1 to 2 years. If a patient has risk factors such as family history or genetic predisposition, then she should discuss screening with her physician.

New guidelines from the USPTF recommend mammography every 2 years for women over age 50. They do not recommend screening women aged 40 to 49, although 2 years ago, the American College of Physicians recommended optional mammograms for women aged 40 to 49. High-risk women (two first- or second-degree relatives who developed breast cancer before age 50 or three first- or second-degree relatives who developed breast cancer at any age or had a known gene mutation) should discuss with their physician the risks and benefits of routine screening. If a patient has a life expectancy of at least 10 years, then she should continue mammography every 2 years.

**DR HALY:** For high-risk women, the ACS recommends annual screening with mammography and magnetic resonance imaging (MRI) beginning at age 30. In July 2017, the American College of Obstetricians and Gynecologists revised their recommendations to emphasize patient and provider shared decision-making. The recommendations (http://www.contemporaryobgyn.net/breast-cancer/breast-cancer-risk-assessment-and-screening) are that women at average risk of breast cancer should be offered screening mammography starting at age 40 and should begin screening mammography by no later than age 50. The decision about the age to begin mammography screening should be made through a shared decision-making process including discussion of the potential for false-positive testing requiring additional evaluation and the stress associated with such events. Screening should continue every 1 to 2 years with the interval determined by patient values and preferences. After age 75, the decision to continue screening should be based on the patient’s health status.

**DR LOCKWOOD:** What about 3D imaging, which is now covered by Medicare?

**DR LYNCH:** 3D imaging is also called tomosynthesis. That technology was created to overcome some of the drawbacks of standard mammography. From the patient’s perspective, she may notice that less tissue compression is required, however, the test takes longer, namely 7 seconds per exam as 11 images are obtained. They are then assembled into a 3D image by a computer. Because it takes a little longer to get the images, Aase et al recently published an interim analysis of their randomized controlled trial of digital breast tomosynthesis vs digital mammography and found that there was no difference in radiation dose between the two and no difference in the call-back rate for women with dense breasts (3.6% for both). In women with non-dense breast, however, the recall rate was decreased to 2%.
The American Heart Association changed the systolic blood pressure cut-off...the new guideline (for diagnosis of hypertension) is 130/80 mmHg.

2.2% for digital breast tomosynthesis compared to 3.4% for digital mammography. \( P = 0.04 \).\(^5\)

**DR HALY:** MRI of the breast is the most sensitive test for breast cancer detection, however, the cost and time needed to perform it limits widespread use as a screening tool. There are current efforts, however, evaluating abbreviated dynamic contrast-enhanced (DCE) MRI protocols, so this will be something to keep an eye on for the future.\(^6\) Until then, MRI is limited to being performed for patients at high risk or women diagnosed with breast cancer to determine the extent of disease. There is no radiation exposure with MRI.

**Cardiovascular disease**

**DR LOCKWOOD:** Everyone is worried about cardiovascular disease (CVD). As physicians, we need to get a complete history from patients because women who have early-onset preeclampsia are at risk for CVD later in life.

**DR HALY:** Absolutely. We need to take a complete obstetrical history. Women with early-onset preeclampsia during pregnancy are at increased risk of developing CVD later in life. They have a more than 2-fold increased risk of dying from CVD later in life. Screening women with early-onset preeclampsia 9 to 16 years after index pregnancy found 42% of them could meet criteria for preventive measures, compared to 14.3% of healthy controls.\(^7\) Women who develop earlier onset preeclampsia (before 36 weeks’ gestation) or have multiple hypertensive pregnancies are at highest risk (RR, 3.4 to 8.12).\(^8\) These women did not have coronary artery disease (CAD) but did have risk factors that could lead to CAD/CVD. They may be at risk for hypertension, diabetes, CVD, and CAD, which can allow us to risk modify at an earlier age.

**DR LOCKWOOD:** Diabetes is prevalent in our society. Let’s talk about how we screen for it.

**DR HALY:** Starting at age 45, patients should be screened with a baseline fasting blood sugar and then have screening repeated thereafter at least every 3 years. Patients who are overweight or have risk factors for diabetes need to be screened every year.

**DR LYNCH:** In 2013, the A College of Cardiology and the AHA recommended using a risk-based approach to prescribing statins. Ob/gyns should use the risk calculator (cvrisk-calculator.com) instead of low-density lipoprotein levels to determine whether use of statins is warranted. If a patient has a 10-year risk between 5% to 20%, then the Society for Cardiovascular Computed Tomography recommends coronary artery calcium scoring to determine need for statin therapy.\(^10\)

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Continued on page 29
In January 2018, Contemporary OB/GYN launched a year-long series to bring maternal mortality to the forefront of our coverage. Under the guidance of Editor-in-Chief Charles J. Lockwood, MD, MHCM, and the two of us, as Series Editor (CMZ) and Executive Editor (LMW), respectively, caregivers were alerted to this crisis, terminology was defined and clarified, and the problem dissected one layer at a time (http://www.contemporaryobgyn.net/article/maternal-mortality-special-series). We exposed etiologies through detailed topical presentations, providing cutting-edge pathophysiology as well as algorithms for caregivers to enhance safety (http://www.contemporaryobgyn.net/maternal-mortality-etiologies-and-risk-factors). We provided resource lists that expanded on the information we presented, and we provided resource guides to educate patients and their families on crucial information (http://www.contemporaryobgyn.net/maternal-mortality-additional-reading-and-resources). We provided articles on the tragedy of maternal loss and how it affects families left behind as well as the physicians who are also touched by the loss (http://www.contemporaryobgyn.net/maternal-mortality-special-reports).

We are proud of this year’s work, but also aware that the crisis of maternal morbidity and mortality can’t be covered completely within the span of 12 issues. We owe it to our mothers to keep going. Therefore, Contemporary OB/GYN is committing to continued coverage of maternal mortality into the new year and beyond, as significant developments arise.

Solutions to the maternal mortality crisis require implementation of strategies at every level, starting with ob/gyns as individuals and as members of the local care community. Staying up to date with the latest research on maternal mortality and morbidity and being aware of and adhering to best practices are a start. Supporting institutions in their implementation of bundles, toolkits, protocols and guidelines, and participating in multidisciplinary drills, reviews, and training sessions in emergency, labor and delivery, and postpartum units would be even better. Ob/gyns who want to take an even larger role can initiate case studies of their local patient population and coordinate with local chapters of the Maternal Mortality Review Committees (MMRCs) and other agencies.

As practitioners, we should also be aware of other health care models.
Seeing is Believing:
The Power of Direct Visualization

Increasingly, hysteroscopic resection is replacing blind biopsy and dilation and curettage (D&C) to identify and remove pathology. What does this mean for patients and clinicians?

In this podcast, Serena H. Chen, MD, examines the risks associated with removing fibroids and polyps through blind biopsy and D&C, underscoring the importance of direct visualization provided by hysteroscopy.

Listen now at contemporaryobgyn.net/visualize
that have successfully lowered maternal mortality in other countries. The UK success story is worth examining in more detail as summarized by Knight and Tuffnell.\(^1\) The UK reduced maternal mortality from 14/100,000 maternities in 2004 to 8.5/100,000 maternities in 2014. While a direct cause and effect cannot be proven, the UK’s success in reducing maternal mortality appears to be linked to detailed surveillance and structured root cause analysis (RCA) case reviews performed by the Confidential Enquiry into Maternal Deaths (CEMD), now in its 60th year of existence. The current project to halve maternal deaths is a pattern that other countries, including our own, can emulate.

As we have learned, publication of a clinical pathway alone does not ensure adherence at the bedside, either in a particular care setting or in every state in the country. Commitment to lowering maternal mortality will require dedication of practitioners as well as relentless engagement of healthcare systems that value individuality and embrace our diversity as a nation. By working together, we can develop and implement the standards necessary to safeguard the lives of our mothers, one life at a time.

REFERENCE

Well-woman exam CONTINUED FROM PAGE 26

Screening for osteoporosis

**DR HALY:** We all know how dangerous hip fractures can be as we age. Bone density testing should be performed in women over 65 and men over 70 with no risk factors. Follow-up testing should be done every 2 to 5 years depending on risk. Ob/gyns should use the FRAX (Fracture Risk Assessment Tool) guidelines to evaluate 10-year risk of fracture (https://www.sheffield.ac.uk/FRAX/).

We hope the information discussed here will be of help to ob/gyns in their practices. This is, of course, not all-encompassing but it is a resource to help you with some of the new guidelines in caring for your patients.

**REFERENCES**


Maternal health in the United States is in crisis. There are almost 4 million births every year in this country. Delivery is the most frequent cause of hospitalization, and cesarean deliveries remain the most common surgery performed, and the United States spends almost twice as much as other high-income countries on medical care. Yet, more mothers are dying from pregnancy-related causes in this country than in any other high-income country. Every year in the United States approximately 700 women die from pregnancy-related causes.

Even more concerning is the fact that maternal death rates in the US have doubled over the last 20 years, albeit partly due to improved ascertainment, while other high-income countries have reduced their rates. As maternal deaths rise, so, too, do severe complications from childbirth. For every maternal death, over 100 women suffer severe maternal morbidity, resulting in over 50,000 women every year experiencing a life-threatening complication related to childbirth. Pregnancy and childbirth are often framed as organic stages in a woman’s reproductive journey, but these numbers and statistics make it evident that healthy outcomes for mothers are not guaranteed.

Our poor performance in reducing US maternal mortality rates is linked to significant and persistent racial and ethnic disparities. Maternal morbidity and mortality rates in the US are linked to significant and persistent racial and ethnic disparities. Recommendations are based on lessons from other areas of medicine as well as expert opinions, quality improvement science, and extensive work by patient safety and women’s health care organizations.

Despite these alarming trends in maternal mortality and severe maternal morbidity rates and entrenched racial and ethnic disparities in such outcomes, 60% of pregnancy-related deaths and severe maternal morbidities in the United States are thought to be caused by environmental, social, and economic factors related to poverty and racism.

DR HOWELL is director of The Blavatnik Family Women’s Health Research Institute, Mount Sinai Health System vice chair for research and professor in the Department of Obstetrics, Gynecology, and Reproductive Science at Icahn School of Medicine at Mount Sinai, New York.

MS AHMED is a medical student at Icahn School of Medicine at Mount Sinai, New York.

Step-by-step plan to reduce racial and ethnic disparities in care

Eight steps for narrowing the maternal health disparity gap

by ELIZABETH A. HOWELL, MD, MPP, AND ZAINAB N. AHMED, BA
be preventable. A recent Centers for Disease Control and Prevention (CDC) review of maternal deaths across nine states found that the deaths were related to clinician, facility and system factors, such as inadequate training, missed or delayed diagnosis of complications, poor communication and lack of coordination between clinicians. These findings and others reinforce the fact that any efforts to reduce maternal mortality must focus on ensuring quality and safety of maternity care for all women. Further, given the entrenched racial and ethnic disparities in these outcomes, these efforts must also be rooted in health equity. The purpose of this article is to frame the maternal mortality crisis and identify ways to narrow the racial/ethnic disparity gap within a quality of care framework.

Definitions
The World Health Organization defines maternal mortality as the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by pregnancy or its management but not from incidental or accidental causes and this is the definition utilized for international comparisons. A pregnancy-related mortality is defined as the death of a woman while pregnant or within 1 year of termination of pregnancy from causes related to the pregnancy and this statistic is monitored by the CDC.

Health disparities are defined as “a particular type of health difference that is closely linked with economic, social or environmental disadvantage.” Many experts have emphasized the importance of clarity about the concepts of health disparities and health equity and stressed the underlying notion of social justice. A useful definition is one by Dr. Paula Braveman: “Health equity and health disparities are intertwined. Health equity means social justice in health (i.e. no one is denied the possibility to be healthy for belonging to a group that has historically been economically/socially disadvantaged). Health disparities are the metric we use to measure progress toward achieving health equity.”

Contributing factors
Developing targeted and actionable interventions requires untangling a complex web of factors that contribute to racial disparities in maternal healthcare. It is useful to conceptualize the components that contribute to maternal death as consisting of a vertical dimension, representing agents involved in the healthcare system from institution to individual, and a horizontal dimension comprising a longitudinal continuum of care, from preconception to maternity and beyond, including the postpartum period and inter-pregnancy intervals. The intersections between the horizontal and vertical elements represent touch points between mother and clinicians that shape and determine the patient’s health outcome.

Using this conceptual framework, we can start at the individual level. A patient has a set of intrinsic characteristics that determine her health status. Patient factors include non-modifiable items like age and race and are also linked to social determinants of health, including education, literacy, employment and poverty, which ultimately mold a patient’s knowledge, beliefs, and perceptions of health. The external environment also informs a patient’s health status. Women living in poorer communities and neighborhoods often have less access to healthy foods and safe parks, are exposed to more toxins, and are at higher risk for poor perinatal outcomes.

Comorbid illnesses complicate a patient’s medical story even more and women from racial and ethnic minority communities have a higher prevalence of common diseases like hypertension, diabetes, and obesity.

It is important to note the ways in which structural racism have shaped the health and opportunity for women of color. Historical and economic forces, including restrictions on housing options, jobs and education, have entrenched women who belong to racial and ethnic minority groups in cycles of marginalization and inequality. Social determinants are important contributors to racial and ethnic disparities in maternal outcomes, but they do not fully explain the higher rate of maternal death and severe maternal morbidities among racial and ethnic minority women. For example, in New York City, a black woman with a college education is almost three times as likely to suffer severe maternal morbidity as a white woman who has less than a high school education (Figure 1).

Clinicians, including nurses, midwives and doctors, as well as support persons such as doulas, are partners in a patient’s health throughout the course of her life. A clinician’s knowl-
edge and experience contribute to a patient’s preparedness and comfort with her pregnancy, labor and delivery and the postpartum period. This relationship can be influenced by implicit bias, cultural competence and communication skills. Implicit bias refers to behaviors in reaction to a patient’s characteristics like age, race, ethnicity, gender, sexual orientation, physicality, and disability that shape our behavior and actions and informs clinical decisions. These biases are deeply rooted and are deployed unconsciously.

Quality of care for pregnant women is important across the care continuum. Delivery care represents another significant “touch point” between the patient and clinician, where severe maternal morbidity and mortality often occur and where racial and ethnic disparities in maternal outcomes manifest. Data suggest that racial and ethnic disparities in severe maternal morbidity and mortality are due to disparities both within (intra-hospital) and between institutions (interhospital). For example, in the United States, nearly 75% of black women deliver at a quarter of all delivery hospitals while only 18% of white women deliver in those same hospitals. Both black and white women have higher severe maternal morbidity rates at those hospitals regardless of patient risk factors.

Intra-hospital differences also contribute to racial/ethnic disparities in maternal mortality rates. In a study examining how racial/ethnic minority-serving hospitals performed on 15 birth-related indicators, significant racial/ethnic disparities in delivery-related indicators were reported within each type of hospital (e.g. black-serving, white-serving). Delivery care is only one part of the care continuum for pregnant women. Preconception care is critical for optimizing contraceptive counseling, management of chronic illness and addressing the health needs of women. There is substantial evidence that racial/ethnic women have less access to preconception care. Antenatal care is crucial to optimizing the health of mom and fetus and we know that access differs across the United States, depending on insurance status and race/ethnicity. Postpartum care has been given less emphasis in traditional frameworks of maternal healthcare and yet this period of time presents a window of opportunity to address both physical and emotional needs of mothers from gestational diabetes to postpartum depression. However, rates of postpartum visits are low: 16% to 36% of women do not attend the 6-week follow-up visit and those who do report inadequate care and guidance at that time.

Eight steps for narrowing gaps

Actionable steps are required if we are to improve maternal healthcare and address the unacceptable racial and ethnic disparities that exist. Many of the recommended steps will improve care for all pregnant women. Additional steps address the unique circumstances that many women of color face when encountering the healthcare system. Although not every initiative has a strong evidence base, the proposed recommendations are rooted in lessons from other areas of medicine, expert opinion, quality improvement science, and the extensive work done by the Council on Patient Safety in Women’s Health Care and the Alliance for Innovation in Maternal Health (https://safehealthcareforeverywoman.org/patient-safety-bundles/reduction-of-peripartum-racial-ethnic-disparities). We present eight recommended steps to narrow disparities within a quality-of-care framework (Table 1).

ENHANCE COMMUNICATION AND IMPLEMENT UNCONSCIOUS BIAS TRAINING.

Improving communication between patient and provider can avoid mismanagement, delays or failure in diagnosis and poor patient advocacy. Shared decision-making is a practice rooted in patient-centered care. It entails a process of weighing patient’s goals, decisions and expectations against clinical guidelines.
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and best practices in an open and honest conversation between patients and clinicians.34 Shared decision-making is necessary to develop and deliver treatment plans that address differences and narrow disparities. Relaying clinical information effectively may require the use of aids and teach-back methods to appropriately convey risk and benefits, given cultural and language barriers.35 Assessing non-English language proficiency and educating staff on the availability and need for interpreter services are important for creating a culture of equity as it relates to patient empowerment and access to knowledge.36 Addressing implicit bias is less concrete but nevertheless needed. Tactics include individuation, or rather “intentionally focusing on individual patients’ information apart from their social group.”37 Implicit bias/unconscious bias trainings are now being offered at some healthcare institutions. Two additional tactics include incorporating cultural competency as part of training curriculums and ensuring diversity in clinicians and staff, both of which will improve the quality of communication skills.38

**IMPLEMENT DISPARITIES DASHBOARD AND PERFORM ENHANCED MATERNAL MORTALITY AND SEVERE MATERNAL MORBIDITY REVIEWS.** To implement a disparities dashboard, a few steps are needed. First, self-identified race and ethnicity as well as language and place of birth should be captured in the medical record. There is evidence on how to train staff to ask these questions and how to best explain to patients why it is important to collect this information.38,40 The next step is to review quality metrics stratified by race and ethnicity to ensure hospitals are aware of their performance for different racial and ethnic groups. Results from the disparities dashboard should be regularly shared with leadership and staff.41 Next, quality improvement tools should be used to address the disparities identified. Ultimately, by putting hospital system performance under review, quality improvement tools can be deployed to narrow the disparity gap. Learning from every death and severe complication is a very important step to preventing future events. As recommended in the recent Alliance for Innovation on Maternal Health (AIM) bundle, multidisciplinary case reviews are an essential part of the process and should consider the role of race, ethnicity, language, poverty, literacy and racism.33

**STANDARDIZE CARE AND BUILD A CULTURE OF EQUITY.** While quality improvement tools are often designed to focus on human error and accordingly, prompt system redesign, they can also address gaping disparities. Given that the majority of maternal deaths and severe complications related to childbirth and deliveries in the United States are preventable, we need to ensure equal standards of care for patients of all racial and ethnic groups. Standardization of care with use of the AIM bundles, such as those directed at hypertension, hemorrhage, and venous thrombotic disease, is a first step in the right direction.32 Utilization of quality improvement tools such as triggers, protocols, drills, evidence-based practices, policies and procedures, checklists, simulation training, and other items is crucial not only for quality improvement initiatives but also for ensuring equal standards across hospitals.37,41,42 Team training is also recommended by various oversight committees, including the Institute for Healthcare Improvement.17

We must promote a culture of equity in our institutions by employing many of the tools we have used to emphasize a culture of safety, in addition to acknowledging, discussing, measuring, monitoring, and utilizing continuous quality improvement efforts to address disparities.32 Reports of inequity, miscommunication, and disrespect warrant careful review to identify system-level opportunities to better meet the needs of racial and ethnic minority population.33

**DEVELOP NEW MODELS OF CARE ACROSS THE CONTINUUM.** New models that promote women’s health across the lifespan need to be developed to address our fragmented healthcare system. Preconception care should include development of a reproductive plan and judgment-free and noncoercive contraceptive counseling25 and address questions and concerns regarding family plan-

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ling. Counseling at this stage allows for early intervention for health conditions and behaviors such as obesity, hypertension, and tobacco use and can ultimately improve patient health status before pregnancy.

Preconception care can also extend to inter-pregnancy intervals with emphasis on childbirth spacing. While prenatal care is known to be crucial for ensuring healthy perinatal outcomes, timing and receipt of prenatal care can be low among low-income women of color. Structuring care differently might yield better outcomes versus traditional models. Group prenatal care models such as CenteringPregnancy provide prenatal care in group settings according to due date and have demonstrated some promising results, though the impact of reducing maternal deaths or severe complications through these initiatives has yet to be studied. They do, however, offer alternative models for health empowerment for mothers through their pregnancies. Similarly, case management and patient navigation programs can assist in coordinating postpartum care, an important touchpoint for women following pregnancy. The importance of comprehensive care in the postpartum period has recently been emphasized by the American College of Obstetricians and Gynecologists (ACOG).

ENGAGE KEY STAKEHOLDERS. Rallying key stakeholders allows for wide implementation of multidisciplinary initiatives to tackle maternal mortality. Stakeholders can include state agencies, organizations like ACOG or the American College of Nurse-Midwives, health care systems, patient advocacy groups, local communities and patients. California has created a model of organizing public-private partnerships through coordinated efforts of the California Department of Public Heath and the California Maternal Quality Care Collaborative (CMQCC). In that state, rates of maternal death have been reduced by one-half (from 13.1 to 7.2 for every 100,000 live births).

The approach included four distinct parts, as outlined by the CMQCC:
1. using public health data to develop quality improvement measures on causes of death and pregnancy-related complication;
2. engaging public and private stakeholders;
3. establishing a data system to track and monitor quality improvement efforts; and
4. affecting change through larger interventions by coordinating between clinical providers and public health services.

Mobilizing the California Department of Public Health, CMQCC, consisting of various stakeholders and the California Pregnancy-Associated Mortality Review committee, created a larger network of ideas, resources, and funding streams. While health equity was not a primary goal of the initiative, California displayed an overall reduction in maternal mortality for all racial and ethnic groups from 1999 to 2001 through 2011 to 2013, although the mortality disparity ratio, the gap between black and white women, remained the same.

Conclusion
Addressing racial and ethnic disparities within the larger maternal mortality crisis requires targeted efforts towards modifiable factors, grounded in healthy equity and quality improvement. Promoting a culture of equity involves addressing implicit bias and individual and systemic racism, while also utilizing quality improvement tools and transforming culture. Enhanced communication, reduced bias, careful monitoring, and improvement of performance for all of our populations and engagement of key stakeholders can begin to narrow the maternal mortality and severe maternal morbidity disparity gaps. Ultimately, these actions will elevate the quality of care received by all mothers, including those who belong to racial/ethnic communities.

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ACA Medicaid expansion and prenatal insurance in low-income women

by JUDITH M. ORVOS, ELS

Lack of insurance may limit patient access to prenatal care. For low-income women, the Affordable Care Act (ACA) and expansion of Medicaid in some states provided a new opportunity for coverage before pregnancy. A new study provides insight into what effect the ACA Medicaid expansion had on preconception insurance coverage among low-income women.

Published in Obstetrics & Gynecology, the study used a quasi-experimental, difference-in-difference design to compare changes in preconception insurance coverage among low-income women living in expansion compared with nonexpansion states before and after the Medicaid expansions. In such a design, longitudinal data are used to compare the effect of an intervention between an exposed and an unexposed group. Differences between the groups are attributed to the intervention.

The 57,056 women included in the study participated in the Pregnancy Risk Assessment Monitoring System from 2009 to 2015. All had family incomes ≤ 138% of the federal poverty level, meaning that they were newly eligible for Medicaid if they lived in expansion states. Of the participants, 30,495 were from eight states that expanded Medicaid under ACA and 26,561 were from seven states that did not.

The primary outcome of the study was insurance status 1 month before conception. The researchers performed additional subgroup and sensitivity analyses to test the assumptions of the model and the robustness of the findings.

Before ACA, 30.8% of women in nonexpansion states had Medicaid coverage prior to conception versus 35% after ACA. Of the women in the states where Medicaid was expanded, 43.2% had Medicaid coverage prior to conception before ACA versus 56.8% after the expansion. There was a significantly greater increase in Medicaid coverage in expansion states after the policy implementation (adjusted difference-in-difference estimate +8.6% points, 95% CI 1.1–16.0).

Rates of preconception uninsurance were 44.2% prepolicy and 34.3% postpolicy in nonexpansion states and 37.4% prepolicy and 23.5% postpolicy in expansion states. Changes in uninsurance did not differ significantly between the two groups in the postpolicy period. Non-Medicaid insurance coverage was 25.3% prepolicy and 30.5% postpolicy in nonexpansion states and 19.4% prepolicy and 19.7% postpolicy in expansion states.

The authors concluded that Medicaid expansion was associated with increased enrollment in Medicaid before pregnancy among low-income women and “with greater continuity of Medicaid coverage from the preconception to pregnancy period.” To fully assess the effects of the policy change, they said, more years of postpolicy data are needed while noting that their analysis relied on self-reported survey data collected after delivery, which could be subject to recall bias.

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

More well-woman information in “Key points for today’s well-woman exam” on PAGE 23
Violence against women is a major public health issue and an estimated 25% of women will experience intimate partner violence (IPV) or sexual assault in their lifetime. In addition, 1 in 10 women will develop posttraumatic stress disorder (PTSD) after these or other traumatic experiences. Studies have found that IPV, sexual assault and PTSD can have long-term effects on health and may compound the effect of aging-related health problems. However, most research is focused on reproductive-age rather than midlife and older women.

A cross-sectional analysis, recently published in *JAMA Internal Medicine*, examined how common IPV, sexual assault, and PTSD are among this population and whether these exposures are associated with a woman’s menopause experience.

The participants were members of Kaiser Permanente Northern California (KPNC), approximately 20% of whom were purposefully recruited from the KPNC Diabetes Registry. Data on exposures and outcomes were based on self-administered or interviewer-administered questionnaires that assessed lifetime IPV and sexual assault exposure. Positive responses were further probed to assess IPV in the previous 12 months and the participant’s age at the last occurrence of sexual assault. Symptoms associated with menopause were assessed using interviewer-administered structured-item questionnaires. The authors prioritized three types of symptoms associated with the menopause transition: difficulty sleeping, vasomotor symptoms, and vaginal symptoms.

Of the participants, 792 (39.4%) were non-Latina white, 429 (21.3%) black, 403 (20.0%) Latina or Hispanic, and 387 (19.2%) were Asian. The women were largely postmenopausal (1643 of 2002, [82.1%]) and had a mean age of 60.5. A majority were overweight and had at least some college education. Fewer than 10% had clinically significant depressive symptoms and 18.4% reported anxiety.

Lifetme emotional IPV was reported by 423 women (21.0%), lifetime physical IPV was reported by 316 (15.7%), and 256 of 1790 women (14.3%) reported both emotional and physical IPV. Sixty-four women reported IPV within the past 12 months. Sexual assault was reported by 382 women (19.0%) and nearly three-quarters of the attacks occurred when the victims were younger than 25. Overall, 22.5% of women met criteria for current clinically significant symptoms of PTSD. The authors also noted significant variation between the rates of lifetime IPV and sexual assault between racial/ethnic groups, with Asian women reporting the lowest rates. However, there were no significant difference among observed rates of PTSD across racial/ethnic groups.

In regard to menopause symptoms, 1148 women (57.1%) reported difficulty sleeping, 802 (39.9%) reported hot flashes, 692 (34.4%) reported night sweats, 633 (31.5%) reported vaginal dryness, 260 (12.9%) reported vaginal irritation, and 257 of 1457 sexually active women (17.6%) reported pain with intercourse. The authors observed significant variation in rates of some menopausal symptoms with vasomotor symptoms most common among black women.

Looking at associations between traumatic exposures and menopause symptoms, the authors found that women who had lifetime emotional IVP were more likely to report difficulty sleeping, night sweats and pain with intercourse. Women who reported lifetime physical IPV were more likely to have night sweats and pain with intercourse. Women who reported lifetime sexual assault were more likely to have vaginal dryness, vaginal irritation, and pain with intercourse. Symptoms of PTSD were associated with all menopause symptoms (difficulty sleeping, hot flashes, vaginal dryness and irritation, and pain with intercourse.)
A few strengths and limitations to the study were observed. Among the noted limitations were that longitudinal trends, including elapsed time since the trauma, duration or chronicity of menopause symptoms and traumatic exposures, cannot be determined from the data. It is also unknown whether assessed symptoms of PTSD are associated with reported IPV and/or sexual violence among women with both exposures. The authors were unable to determine whether participants had disclosed traumatic experiences, had previously identified diagnoses of PTSD, and/or had previously engaged in trauma-focused treatment. Strengths of the study include characterizing varied aspects of the experience of menopause symptoms, traumatic exposures and symptoms of PTSD in a large, ethnically diverse cohort.

The authors believe that their findings illustrate that IPV, sexual assault, and symptoms of PTSD may be associated with development and experience of menopause symptoms. While menopausal symptoms are largely related to biological and hormonal changes related to menopause and aging, a woman who has experienced IPV or sexual assault may have alterations in her physiological response to stress. These changes may make her more susceptible to symptoms of aging and menopause. The results from this study also reinforce the need for better recognition of these exposures by clinicians caring for middle-aged and older women. They also suggest a need for stronger efforts to provide better and more informed care to all women across the aging spectrum who are suffering from traumatic exposure.

Ben Schwartz is the associate editor for Contemporary OB/GYN
Before physicians decide to join a practice or a hospital, they should know if doing so aligns with their professional and personal goals. This is an important decision, and before they make it, doctors should do the necessary research to determine if their prospective new employer is right for them.

Understanding culture in a large practice

Doctors should get a feel for the culture of the new employer—i.e., its internal dynamics, how people relate to one another, and if there is life after office hours. “You’re looking at whether or not you like the individual physicians in the group,” says Russell Still, CVA, CHBC, executive vice president of Medical Management Associates, a healthcare consulting firm in Atlanta that provides management resources and counsel for physicians in private practice. “You want to find out if they’ve had other employed physicians and, if they’re not there anymore, you want to talk to them to find out why they left.”

The new doctor also should understand the work ethic of the physicians who lead the organization. “If you’re looking for balance in your life, do they have balance in theirs?” asks Still. “Are they just working all the time?”

How decisions are made, and by whom, and how much autonomy and decision-making power doctors have is a critical cultural issue. “Ask if decisions are made by physicians or by business people in the boardroom,” says Robert M. McLean, MD, FACP, president-elect of the American College of Physicians and medical director of clinical quality for the Northeast Medical Group, in New Haven, Conn.

While McLean thinks that non-physicians may be qualified to make those decisions at times, he nevertheless says that “frequently, doctors have more trust in physicians making the big management decisions. That often is a major cultural factor.”

If doctors want to be part of the management structure, they should say that up front. “You should be very clear that you want to be more participatory and exercise some leadership,” says Scott Joy, MD, MBA, FACP, medical director of Colorado Care Partners and chief medical officer of the Continental Division of the HCA Physician Services Group in Denver.

“During the negotiation, ask what committees you can serve on—such as EHR or quality improvement,” Joy says. “You’re going to have better opportunities to be on committees by making that part of the contract that you negotiate.”

Doctors should ask the practice leaders why they want to hire a new member. “You’d be surprised, but sometimes people don’t ask why...”
they’re looking,” says Wanda Parker, a principal with the HealthField Alliance, in Danbury, Conn.

Parker also suggests doctors ask prospective employers about their expectations for a new employee or associate—i.e., what duties do they want the new doctor to assume? How many and what types of patients do they want the doctor to see? What are their long-term goals for the doctor? What are the quality metrics they want the doctor to satisfy? How will the doctor mesh with the other physicians and non-physician members of the staff?

Culture also includes what doctors are allowed to do aside from seeing patients. Can they teach or do research or donate their services elsewhere?

“Sometimes they don’t want people to do outside activities because they feel it detracts from their commitment to the practice,” says Parker. “In other cases, the practice will be absolutely thrilled if the doctor volunteers for the local football team to be their sports medicine doctor.”

**Buy-in vagueness and other red flags**

Investigating the organization’s culture also should help doctors detect any problems that might dissuade them from signing on. A huge warning sign is any vagueness or reluctance about spelling out the precise conditions, and costs, of becoming a partner in the future.

“The big red flag for me is when they won’t talk about the ultimate buy-in to the practice,” says Still. Doctors who get nothing more than a general promise of partnership someday may never attain that status and end up feeling like victims of a bait-and-switch ploy.

**WATCH OUT FOR THESE RED FLAGS**

- Vagueness or reluctance about becoming a partner
- Partnership fee is cost prohibitive
- Vagueness about what happens when a partner leaves the practice
- High turnover in the practice
- Not enough financial resources to allow physicians to do their jobs

If doctors have particular expectations about when and under what circumstances they would become partners, they must protect themselves by getting those expectations spelled out in the contract.

Another potential problem is that the fee a physician ordinarily must pay to become a partner could be prohibitively expensive, where a doctor might have to borrow money to do it.

“Doctors should always know up front what the buy-in’s going to be and how it’s going to be calculated,” Parker says. “And what happens when one of those partners leaves? Will they have to buy that person out?”

Frequent turnover, either among staff, the leadership or physicians, is another worrisome indicator, according to Joy.

“If your average tenure of a doctor is a year and a half, that’s not good,” he says.

Average tenures can vary, where doctors leave for personal reasons, differences with the practice leaders, or, increasingly, the desire to remain independent instead of staying with groups that affiliate with hospitals/health systems. There really isn’t a set average tenure for group practices, though Still suggests a new doctor may be with the practice for 2 to 4 years before becoming a partner.

“Doctors should ask about how long the practice manager’s been there and what the average staff and physician turnover are.”

A parallel concern is when a practice that may be financially pressed skimps on staff to save money and thereby makes it harder for physicians to do their work.

“If you don’t have enough care coordinators or medical assistants to do some of the data management legwork, it’s going to be really hard to meet some of the quality metrics,” says McLean. The best way to find out about staffing levels is to ask and, if given a tour of the office, request a tour during work hours, be aware of how many staff are present, take notes and ask about staff functional responsibilities. Focus particularly on the front desk and clinical assistants – the staffers who are essential to the patient’s office visit.

**Compensation and contracts**

Not only should doctors know what their pay will be and how it’s determined, they should understand exactly what their contract means, and what issues the practice is willing to negotiate up front.

Still says it’s possible to find out the local pay rates for physicians who do similar work, and advises hiring a consultant who has access to survey data or works in physician hiring not only in your specialty but in the local market. That information might also be available online from sources such as the American Medical Group Association or a compensation and benefits analy-
sis firm such as Sullivan & Cotter, or at a local library.

Moreover, doctors should know what formula a prospective employer uses to determine salary and other benefits. “How much of the formula is balancing productivity expectations versus other things—around quality and value, data, oversight and management—that take time and energy?” McLean says.

Also, is some of the compensation formula based on quality bonus payments and shared savings contracts? In that regard, McLean offers a hypothetical example: If the insured savings that totaled 70 percent of a practice’s shared savings in a given year are completely gone the following year, would the practice try to compensate for that loss by cutting back or eliminating quality bonuses.

Determining the compensation isn’t always as simple as quoting a flat-rate salary.

“Sometimes, if you have a higher guarantee, you’ll be paid at a lower RVU rate,” says Joy. “If you want a higher RVU rate, you get a lesser guarantee. You also want to ask about signing bonuses and CME bonuses that are available.”

Flat-rate salaries sometimes are offered, but many practices offer additional pay based on collections in excess of a threshold—usually the new physician’s direct costs divided by the income rate.

Contract stipulations such as restrictive covenants (i.e., contract provisions restricting the future conduct of the doctor, such as competing with the practice for a certain period after leaving it, or soliciting or engaging with patients of that practice after leaving it) and non-compete clauses might seem problematic, but Still says doctors should expect them, and not sign an agreement if they intend to break it later on.

“If you don’t think it’s fair, then don’t sign,” he says. “Work it out or go somewhere else.” And not all such covenants and clauses carry the same legal weight. “Are they really enforceable in your state based upon precedent?” McLean asks.

To find that out, doctors should consult attorneys with specific experience litigating that type of contractual language. Also, enforceability can depend upon factors such as the practice specialty and location, the specific circumstances of a doctor’s termination, and if a court feels that a non-compete clause is unreasonable (e.g., preventing a doctor from practicing in a territory that’s much larger than the area from which a practice derives most of its patients).

Termination clauses can be deceptive, as when doctors negotiate multi-year contracts that they think keep them safely employed for that period.

“What they don’t realize is the contract is only as long as their termination clause, so if the termination clause is 90 days, then your contract is really a 90-day contract,” Parker says. “And then what happens if bonuses are due and the person is terminated?”

While a no-cause notice provision might seem to undermine the value of having a contract, there are other aspects of the relationship that require contract protections for both parties, such as designated responsibilities and salaries. “With no contract, doctors could be fired at any moment,” Parker cautions.

Both no-cause and for-cause termination clauses can be tricky. Doctors should particularly beware of broad statements like “failure to follow the policies of the practice,” because they might be unaware that they’ve done anything wrong. Ideally, those policies should be spelled out.

Still advises that if there is a vague, unclear or confusing contract clause that could create a misunderstanding, where a doctor could unwittingly violate a policy, the doctor should seek contract language to clarify the meaning of the clause. Otherwise, the doctor is subject to the practice’s interpretation of the provision in question.

To sidestep these potential contractual minefields, doctors should hire a healthcare attorney who is steeped in healthcare law to review the contract and assist with the negotiations, says McLean.

### Hospitals can be a different story

In some ways, working for a hospital can be like working for a medical practice, but in other ways it can be quite different. In weighing the relative merits of joining a private practice or a hospital, doctors should take those differences into account.

A hospital might be less accommodating than a group practice in the way it treats a doctor. “You go to work for a hospital and it’s all about business decisions and profitability, and if things

As with a medical practice, it’s important to know if physicians or non-physicians are calling the shots at a hospital.
aren’t working, they’re more likely to fire you than a practice would,” says Still.

As with a medical practice, it’s important to know if physicians or non-physicians are calling the shots at the hospital. McLean implies that hospitals headed by non-physicians may be lower in quality.

“Are enough physicians making decisions to have a medical perspective on healthcare delivery?” asks McLean, who notes that studies show that most of the top 100 healthcare systems are led by physicians. “Having physicians in charge might make doctors more comfortable.”

Contract terms likely are less negotiable with hospitals. “In a hospital situation, where you might have 50 employed doctors, you’re going to get a cookie-cutter contract which says you’ve got 4 weeks of vacation and 1 week of CME and here’s your salary,” says Parker.

Sometimes, doctors can have the best of both worlds by joining a private practice that has close relations with a hospital by virtue of having its offices on the hospital campus. These can include perks like preferred parking, free meals in the physician dining room and CME classes, as well as opportunities for personal growth.

Joy, who works on a medical center campus, says doctors in larger and specialty-based practices with that kind of proximity to a hospital can develop productive relationships with the hospital leadership.

While this wouldn’t necessarily involve admitting patients, doctors instead could get to know hospital leaders through service on committees and participate in the leadership’s outreach into the community. In that way, physicians could make themselves known in that community.

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be performed in another state, due to the gestational age of the pregnancy. The patient elected to continue the pregnancy. The patient delivered at 38 weeks’ gestation by cesarean. The babies had hypotonia, micrognathia, short limbs, and dysmorphic facies. Ultimately, the babies had feeding difficulties and significant growth and developmental delays.

A suit was filed against the following physicians:

- The radiologist for missed diagnosis and misinterpretation of the images
- The consulting gynecologist/reproductive endocrinologist (REI) who not only ordered the MTX, but had performed the patient’s IVF, for misdiagnosis of the patient’s IUP, negligent use of methotrexate, and wrongful birth (allowed in this jurisdiction or state), which is a cause of action on behalf of the parents of a child or children with abnormalities that, had the parents known, they would have either terminated the pregnancy or avoided conception altogether, and
- The first MFM subspecialist for negligent counseling and wrongful birth.

The second MFM was not sued and was ultimately subpoenaed as a fact witness (merely reading the notes from his office chart) for the plaintiff.

The defense attorney had difficulty finding a defense expert, finally identifying an ob/gyn willing to testify on behalf of the physicians. However, several reviewing physicians made recommendations for settlement, as they identified several breaches of the standard of care, and to limit potential damages. The defendant physicians were insured by the same malpractice company that, to reduce frivolous lawsuits, had adopted a policy of taking every case to trial rather than settle.

The case went to trial with the following pertinent testimony:

The plaintiff’s expert testified that, with a history of IVF, a twin gestation was more likely. Thus, high levels of hCG without a demonstrable IUP is not uncommon. The patient was stable, thus immediate intervention was unnecessary. If follow-up hCG levels and ultrasounds had been obtained, the correct diagnosis of an intrauterine twin gestation would have been made. Further, MTX was the proximate cause of the observed fetal anomalies. The REI was negligent in administering MTX without a definitive diagnosis, and the MFM was negligent in providing inadequate and inaccurate counseling as to the risks of MTX. Had the patient been appropriately counseled early in the gestation, she would have terminated the pregnancy.

The defense expert testified that use of MTX for treatment of suspected ectopic pregnancy is within the standard of care. Risk of fetal anomalies with MTX is low and the patient received appropriate counseling and signed a written consent for use of the drug (see Figure 1 for example). A geneticist testifying for the defense reviewed the anomalies associated with MTX use, emphasizing that risk of pregnancy loss was greatest when given very early in pregnancy, while risk of fetal anomalies was greatest if MTX was given at 6 to 10 weeks’ estimated gestation, not when it was given in these patients.

A plaintiff dysmorphologist testified as to the potential fetal abnormalities associated with MTX, and correlated the abnormalities found in the twins and those associated with MTX use.

The defense then stated that the patient had a normal ultrasound at 16 weeks’ gestation and because the pregnancy was highly desired, would not have terminated it when anomalies were identified at 26 weeks’ gestation. Alternatively, the patient could have still terminated her pregnancy (although not in this state) at 26 weeks’ gestation. Further, she signed and consented to use of MTX.

The plaintiff testified she would have terminated had she known of the risks earlier in pregnancy. At the time the abnormalities were identi-
fied at 26 weeks, she ethically could not terminate the pregnancy. Finally, the plaintiff expert testified that, despite the signed MTX consent form, one cannot consent a patient to negligence.

Various life and actuarial experts for the plaintiff testified that the babies would likely live to 72 years of age, would require extensive, lifetime support, and that the patients had suffered tremendous pain and suffering, a claim that had no caps in this state.

The jury came to the following verdicts:

- **Radiologist:** Defense verdict (not guilty)
- **REI:** Plaintiff verdict (guilty) for misdiagnosis of ectopic pregnancy/twin gestation and negligent use of MTX
- **MFM:** Plaintiff’s verdict (guilty) for negligent counseling and wrongful birth.

The jury recommended a total award of $73 million, including long-term support and therapy of two infants with anticipated life-span of 72 years and an award for pain and suffering for the parents. This jurisdiction (the state where the trial took place) recognizes joint and several liability, which means either guilty party can be liable for the entire judgment.

Fortunately, the defendant physicians, when being advised of the difficulty finding experts and the potential financial risk, consulted their own attorneys who asked, documented in writing, that the insurance carrier settle within the limits of the physi-

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**FIGURE 1** Example of a Methotrexate information/consent form

**Treatment of Ectopic Pregnancy with Methotrexate Patient Information and Consent**

You have been diagnosed with an ectopic pregnancy, or a pregnancy in the fallopian tube. Pregnanies in the tube cannot develop normally. The pregnancy cannot be moved from the tube to the uterus, or womb. Options to treat an ectopic pregnancy include observation, surgery, and medications.

- **Observation** may not be recommended as the tube can rupture or burst if the pregnancy continues to grow. This can create a situation where emergency surgery is required. There are reports of women dying from a ruptured ectopic pregnancy.

- **Surgery** is usually performed via a laparoscope, or lighted tube, which most people know as “belly button surgery.” This surgery involves either removing the tube, removing a portion of the tube where the pregnancy is located, or removing the pregnancy from the tube and leaving the remainder of the tube.

- **Medical treatment** involves one or two injections with methotrexate, a medicine that blocks chemicals critical to pregnancy development. In most cases surgery can be avoided with the use of methotrexate.

**Effectiveness** In properly selected patients, methotrexate successfully treats ectopic pregnancies in 95% of patients.

**Blood tests** Blood tests are required before treatment to determine if your liver and kidneys are functioning normally. Additional blood tests will be drawn at 4 days and 7 days after treatment to determine if the medication is successfully treating the ectopic pregnancy. Following the levels of hCG, the pregnancy hormone, is critical and requires that you keep all follow-up appointments.

**Ultrasound** Ultrasound may be required in the future to determine the status of the ectopic pregnancy, if there are any signs of rupture, or if surgery may ultimately be required.

**Side effects** Patients commonly experience increased in abdominal pain during the first week after receiving the medicine. This pain should not be severe. If it is you should notify us immediately. Rarely patients experience nausea, vomiting, or diarrhea. Even less common is the development of ulcers in the mouth. (This is a very rare side effect when using a single or double dose of methotrexate)

**Risks** Methotrexate is harmful to normal pregnancies. Some birth defects have been described when intrauterine pregnancies have been treated with methotrexate. If you are found to have an intrauterine pregnancy after methotrexate treatment it is recommended to receive counseling to determine if the pregnancy should be terminated.
IUP MISDIAGNOSED

One rarely should make a diagnosis of an ectopic pregnancy at an initial visit unless the findings are definitive, that is a gestational sac with yolk sac and/or presence of an embryo.

Case analysis
This case highlights both medical and legal issues. Medically, misdiagnosis of an ectopic pregnancy as an IUP is not uncommon. Physicians must carefully assess such patients, preferably in person, and collate all available information, including the patient’s history, the laboratory and diagnostic studies, and the patient’s clinical status before reflexively administering MTX. Although the patient’s initial hCG level was greater than the published discriminatory levels, i.e. 3500 mIU/mL, the history of IVF placed the patient at greater risk for a multiple gestation, with resultant higher hCG levels than anticipated. Personally reviewing the ultrasound is recommended, as gynecologists are ultimately responsible for the patient outcome.

The order for the initial ultrasound did not include a history of IVF. Thus, the radiologist’s interpretation and recommendations were appropriate, based on the available information. Had the REI obtained serial hCG levels and ultrasounds, the correct diagnosis of a twin IUP would have been made. Diagnosis of an ectopic can only be definitively made if a gestational sac with a yolk sac and/or embryo is identified outside of the uterine cavity. Otherwise, the patient has either a non-definitive diagnosis or a pregnancy of unknown location. In such cases, if clinically stable, the patient should have serial hCG levels and repeat ultrasound for diagnosis.

One rarely should make the diagnosis of an ectopic pregnancy at an initial visit unless the findings are definitive, that is, a gestational sac with yolk sac and/or presence of an embryo, with or without cardiac activity, outside of the uterus.

The defense attorney later learned that the first MFM had never offered termination to a patient, thus potentially imposing his beliefs against pregnancy termination on this patient, crossing an appropriate barrier in provision of care. Ob/gyns should review the available options with patients, allowing them to make an informed decision regarding their care, without allowing personally beliefs to hinder appropriate counseling. Patients can be referred to other providers if they elect a treatment course that conflicts with an ob/gyn’s personal beliefs and prevents providing such care to the patient.

Many physicians want insurance companies to fight every case, ostensibly to reduce frivolous suits. However, refusing to settle legitimate cases can have unexpected and devastating consequences, as illustrated here. Obtaining outside council was critical for the involved physicians. They received advice to settle the case. Having their own attorneys write a letter to the malpractice carrier to settle within the limits of their policies limited their financial exposure. If a settlement offer had been made and refused, the physicians may still have been liable for the judgment. However, the fact that the insurer refused to offer a settlement transferred the major financial risk to the malpractice carrier.
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.

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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.

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You must have a medical degree and a specialty in obstetrics and gynecology to be eligible for this position. You must hold a current license to practice in any state of the US and be eligible for Board Certification.

Primary duties involve pre-market clinical reviews for a range of medical devices used in obstetrics and gynecology, including maternal/fetal monitoring technology, diagnostic and therapeutic devices for gynecologic cancers, endometrial ablation, fibroid treatment, assisted reproduction technologies, urogynecology, gynecologic surgical tools, fetal surgery, contraceptive devices, etc. Responsibilities include:

- providing evidence-based recommendations regarding clinical trial design for novel devices,
- working as a team member to provide real-world clinical knowledge to other non-clinical staff, e.g., biomedical engineers, chemists, microbiologists,
- providing briefings to management and presentations for the FDA Advisory Panels,
- conducting health hazard evaluations for devices in the postmarket arena,
- providing an in-depth evaluation of clinical safety and effectiveness data, and
- identifying trends, outcomes, and adverse events that may impact public health and safety.

Other duties may include:

- meetings with regulated industry to provide guidance,
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- FDA liaison with professional societies,
- presentations to other Federal Agencies, and
- other duties as assigned.

It is important, that the Obstetrician/Gynecologist have analytical skills or research experience. Such knowledge, skills, and abilities make it an easier professional transition to the premarket review of medical devices. A successful medical officer should base recommendations on sound science, assess the impact of new or changing technology on public health, and communicate well with a multi-disciplinary team of statisticians, engineers, and other scientists.

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Interested candidates should forward a copy of their CV to:

Christine Lee, Assistant Director for Program Operations
E-mail: christine.lee@fda.hhs.gov | 301-796-7060

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A 34-year-old G1P0 presented to the Emergency Department early in the morning with complaints of abdominal pain and vaginal bleeding. She underwent in vitro fertilization (IVF) approximately 2 weeks earlier. A quantitative hCG was 4,654 mIU/mL. An ultrasound was performed in radiology with the following interpretation: “Uterus normal sized with a thickened decidual reaction in the uterus. No fetal pole is identified. There is a moderate amount of fluid in the cul-de-sac. There is a right adnexal mass = 2.2 x 1.9 x 2.1 cm. These findings could be compatible with the presence of an ectopic. Clinical correlation and, if indicated, serial hCG levels and follow-up ultrasound studies should be considered.” The patient was clinically stable, with a hematocrit of 38.9%, her blood type was O positive and her liver function and kidney assessments were normal. After consulting with the patient’s gynecologist and after the patient signed a methotrexate (MTX) consent form, the patient was treated with methotrexate, 80 mg IM.

Blood hCG levels on Day 4 and Day 7 following methotrexate were 16,069 mIU/mL and 42,125 mIU/mL, respectively. An ultrasound at that time revealed a twin intrauterine pregnancy (IUP) with two yolk sacs and possible cardiac activity, consistent with 5 weeks’ gestation. An ultrasound performed 2 weeks later revealed a twin IUP with two yolk sacs, two fetuses, both with cardiac activity, consistent with 7 weeks’ gestation. The patient was referred to a maternal fetal medicine (MFM) subspecialist for counseling regarding the potential risk of MTX exposure and the potential fetal anomalies associated with such exposure.

The patient was counseled about the ultrasound findings in her babies and was offered the option of termination, although this would need to be done by another MFM specialist.

The patient was advised that risks of MTX were very low and fetal anomalies associated with MTX can be seen on ultrasound. The patient was advised that risks of MTX were very low and fetal anomalies associated with MTX can be seen on ultrasound.
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