OVER A YEAR OF PATIENT EXPERIENCE

INDICATION
ORILISSA® (elagolix) is indicated for the management of moderate to severe pain associated with endometriosis.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
• ORILISSA is contraindicated in women who are pregnant (exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss), in women with known osteoporosis or severe hepatic impairment, or with concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil).

WARNINGS AND PRECAUTIONS
Bone Loss
• ORILISSA causes a dose-dependent decrease in bone mineral density (BMD), which is greater with increasing duration of use and may not be completely reversible after stopping treatment.
• The impact of ORILISSA-associated decreases in BMD on long-term bone health and future fracture risk is unknown. Consider assessment of BMD in patients with a history of low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use in women with known osteoporosis.
• Limit the duration of use to reduce the extent of bone loss.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy
• Women who take ORILISSA may experience a reduction in the amount, intensity, or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders
• Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials.
• ORILISSA users had a higher incidence of depression and mood changes compared to placebo and ORILISSA users with a history of suicidality or depression had an increased incidence of depression. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate.
• Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.


*Statistical significance for dyspareunia was not achieved with the 150 mg QD dose of ORILISSA.
OVER 10,000 HCPs HAVE ALREADY PRESCRIBED
ORILISSA FOR MORE THAN 30,000 patients

ORILISSA may be appropriate for patients with unresolved endometriosis pain who have failed first-line medical management options such as one course of birth control or NSAIDs

“On ORILISSA, I have less pain. I hope my experience empowers other women and gives them hope that there are other options out there.”

— Darby, a real patient taking ORILISSA

Hepatic Transaminase Elevations

- In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred with ORILISSA.
- Use the lowest effective dose and instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice.
- Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks.

Reduced Efficacy with Estrogen-Containing Contraceptives

- Based on the mechanism of action of ORILISSA, estrogen-containing contraceptives are expected to reduce the efficacy of ORILISSA. The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown.
- Advise women to use non-hormonal contraceptives during treatment and for one week after discontinuing ORILISSA.

Adverse Reactions

- The most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes.
- These are not all the possible side effects of ORILISSA. Safety and effectiveness of ORILISSA in patients less than 18 years of age have not been established.


Please see Brief Summary of full Prescribing Information on the following page of this advertisement.

Get your patients started with a Savings Card at ORILISSA.com/hcp

Over 10,000 HCPs have already prescribed ORILISSA for more than 30,000 patients.
ORILISSA® (elagolix) tablets, for oral use

INDICATIONS AND USAGE
ORILISSA is a gonadotropin-releasing hormone (GnRH) agonist indicated for the treatment of women with severe primary dysmenorrhea in anticipation of menopause or with a diagnosis of endometriosis with severe symptoms and a desire for fertility.

CONTRAINDICATIONS
Exclude pregnancy before starting ORILISSA or start ORILISSA within 72 hours of onset of menses.

WARNINGs AND PREcautionS
- Evoke pregnancy before starting ORILISSA or start ORILISSA within 72 hours of onset of menses.
- Take ORILISSA at approximately the same time each day, with or without food.
- Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives (see Warnings and Precautions).
- Limit the duration of use because of bone loss (Table 1) (see Warnings and Precautions).

Table 1. Recommended Dosage and Duration of Use

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Maximum Dosage</th>
<th>Treatment Duration</th>
<th>Coexisting Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg once daily</td>
<td>6 months</td>
<td>Dyspareunia</td>
<td></td>
</tr>
<tr>
<td>ORILISSA 200 mg once daily</td>
<td>6 months</td>
<td>Moderate hepatic impairment (Child-Pugh Class B)</td>
<td></td>
</tr>
</tbody>
</table>

Hepatic Impairment
No dosage adjustment of ORILISSA is required in women with mild hepatic impairment (Child-Pugh A).

Bone Loss
ORILISSA contains in women with severe hepatic impairment (Child-Pugh C) (see Contraindications and Use in Specific Populations).

Meningeal Stenosis
Instruct the patient to take a missed dose of ORILISSA on the same day as soon as the patient realizes and then resume the regular dosing schedule.

Hepatic Impairment
No dosage adjustment of ORILISSA is required in women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months.

Hepatic impairment (Child-Pugh B) is not recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months.

CONTRAINDICATIONS
ORILISSA is contraindicated in women who are pregnant (see Use in Specific Populations).

Warnings and precautions
- With known osteoporosis because of the risk of further bone loss (see Warnings and Precautions).
- With severe hepatic impairment (see Use in Specific Populations).
- With concurrent use of strong organic anion transporter polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) (see Drug Interactions).

Warnings and Precautions
Bone Loss
ORILISSA causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible upon stopping treatment (see Adverse Reactions). The impact of these BMD decreases on long-term bone health and fracture risk is unknown. Consider assessment of BMD in patients with a history of osteoporosis or other risk factors for osteoporosis or bone loss, and do not use in women with known osteoporosis. Limit the duration of use to reduce the risk of bone loss.

Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.

Change in Menstrual Bleeding Pattern and Reduced Ability to Conceive Pregnancy
Women who take ORILISSA may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner (see Adverse Reactions). Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders
- Increased rates of depression and mood changes associated with the use of GnRH agonists have been observed in clinical studies of ORILISSA and in other GnRH agonists used in clinical trials to treat prostate cancer. ORILISSA is indicated for the treatment of women with severe primary dysmenorrhea in anticipation of menopause or with a diagnosis of endometriosis with severe symptoms and a desire for fertility. The risks and benefits of ORILISSA should be carefully considered before initiation of therapy (see Adverse Reactions).

Adverse Reactions
Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Common Adverse Reactions:

<table>
<thead>
<tr>
<th>Common Adverse Reactions</th>
<th>Placebo</th>
<th>ORILISSA 150 mg once daily</th>
<th>ORILISSA 200 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose groups</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>37</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Mood altered, mood swings</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Depressed mood, depression, depressive symptoms and/or nightmares</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Percent Change from Baseline in Lumbar Spine BMD at Month 6

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Placebo</th>
<th>ORILISSA 150 mg Once Daily</th>
<th>ORILISSA 200 mg Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM-1</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Percent Change from Baseline</td>
<td>-0.3</td>
<td>-2.8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Treatment Difference, % (95% CI)</td>
<td>-3.9 (-3.0, -2.8)</td>
<td>-3.5 (-2.6, -2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM-2</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Percent Change from Baseline</td>
<td>-0.7</td>
<td>-2.6</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Treatment Difference, % (95% CI)</td>
<td>-1.3 (-1.6, -1.0)</td>
<td>-2.5 (-2.8, -2.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most commonly reported adverse reactions in the extension trials (EM-3 and EM-4) who completed 12 months of treatment with ORILISSA and who had follow-up DXA were back pain (7% with 150 mg once daily, 10% with 200 mg twice daily) and nausea (6% with 150 mg once daily, 10% with 200 mg twice daily) and were dose-related. The majority of discontinuations due to hot flushes occurred within 6 months. Partial recovery of BMD was seen in these subjects (Figure 1).

To assess for recovery, the change in lumbar spine BMD over time was calculated in subjects who remained on treatment for at least 12 months. Partial recovery of BMD in the ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily group for up to 12 months and who were then followed after consents of therapy for an additional 6 months. Partial recovery of BMD was seen in these subjects (Figure 1).

In Study EM-4, if a subject had BMD loss of more than 1% at the lumbar spine or more than 2.5% at the total hip or femoral neck, follow-up DXA was required after 12 months off treatment. In Study EM-4, all subjects were required to have a follow-up DXA 4 months off treatment regardless of change in BMD and if a subject had BMD loss of more than 1% at the lumbar spine or more than 2.5% at the total hip or femoral neck, follow-up DXA was required after 12 months off treatment. Figure 3 shows the change in lumbar spine BMD in subjects in Study EM-3/EM-4 who completed 12 months of treatment with ORILISSA and who had a follow-up DXA 12 months off treatment.

Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 6 Months Off Therapy in Studies EM-3/EM-4

Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 6 Months Off Therapy in Studies EM-3/EM-4

Figure 3. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 6 Months Off Therapy in Studies EM-3/EM-4
ORILISSA also demonstrated a dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) over the treatment period. The incidence of amenorrhea among women who were receiving 150 mg once daily for the first six months of treatment ranged from 6%–17% for ORILISSA 150 mg once daily, 13% for ORILISSA 200 mg twice daily, and less than 1% for placebo. During the second 6 months of treatment, the incidence of amenorrhea increased from 17%–18% for ORILISSA 150 mg once daily and 46%–57% for ORILISSA 200 mg twice daily.

After 6 months of therapy with ORILISSA 150 mg once daily, resumption of menses after stopping treatment was reported by 58%, 67%, and 96% of women within 1, 2, and 6 months, respectively. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 88%, and 97% of women within 1, 2, and 6 months, respectively.

After 12 months of therapy with ORILISSA 150 mg once daily after resumption of menses after stopping treatment was reported by 55%, 91%, and 96% of women within 1, 2, and 6 months, respectively. After 12 months of therapy with ORILISSA 200 mg twice daily after resumption of menses after stopping treatment was reported by 59%, 95%, and 96% of women within 1, 2, and 6 months, respectively.

**Drug Interactions**

**Potential for ORILISSA to Affect Other Drugs**

Elagolix is a weak to moderate inhibitor of cytochrome P450 (CYP) 3A. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A (e.g., indinavir).

**Potential for Other Drugs to Affect ORILISSA**

Elagolix is a substrate of CYP3A, P-gp, and OATP1B1. ORILISSA may increase plasma concentrations of drugs that are substrates of CYP3A (e.g., digoxin).

**Lipid Increases**

Lipid increases occurred within 1 to 2 months after the start of ORILISSA treatment. With ORILISSA 150 mg once daily, 13–52% for ORILISSA 200 mg twice daily and less than 1% for placebo. In Study EM-3 and EM-2, 12% and 1% of subjects with mildly elevated LDL-C, HDL-C, and serum triglycerides were noted in ORILISSA treatment in EM-1 and EM-2, respectively. In Study EM-2, 12% of subjects with mildly elevated LDL-C (130–159 mg/dL) at baseline had an increase in LDL-C concentrations above 40 mg/dL in the treatment with ORILISSA and placebo, respectively. In EM-1 and EM-2, 4% and 1% of subjects with mildly elevated serum triglycerides (150–200 mg/dL) at baseline had an increase in serum triglycerides to at least 900 mg/dL with treatment with ORILISSA and placebo, respectively. The effect of co-administration of drugs that inhibit P-gp or OATP1B1 is not known.

**Endometrial Effects**

Endometrial biopsies were performed in subjects in Study EM-1 and its extension and in Study EM-2. The results were consistent with endometrial biopsy findings reported in other endometriosis treatments. ORILISSA treatment did not result in changes suggestive of hyperplasia or cancer. The incidence of endometrial hyperplasia or cancer was 0.4% of ORILISSA-treated subjects and 0.5% of placebo-treated subjects.

**Hepatic Transaminase Elevations**

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), 10% to 12% of subjects reported hepatic transaminase elevations. In Study EM-3, 150 mg once daily, and in one in Phase 2, 200 mg twice daily, an uncommon anorgan analysis. These subjects had no recent relevant medical history. Stress was noted. Among the 2030 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicidal ideation. In addition to the two subjects in Table 4, there were two additional reports of suicidal ideation; one subject in EM-1 (150 mg once daily) and one in a Phase 2 (200 mg twice daily) study, an unexplained death. Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment period.

**Potential for Suicidal Ideation and Suicidal Behavior in Studies EM-1 and EM-2**

Table 4. Suicidal Ideation and Suicidal Behavior in Studies EM-1 and EM-2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Suicidal Ideation</th>
<th>Suicidal Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORILISSA 150 mg once daily</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>ORILISSA 200 mg twice daily</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Adverse Reactions**

**Oral Contraceptive (OC) Users**

In one study of 3 years of ORILISSA 150 mg once daily then completed suicide 2 days after ORILISSA discontinuation. She had no recent relevant medical history. Stress was noted. Among the 2030 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicidal ideation. In addition to the two subjects in Table 4, there were two additional reports of suicidal ideation; one subject in EM-1 (150 mg once daily) and one in a Phase 2 (200 mg twice daily) study, an unexplained anorgan analysis. Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment period.

**Oral Contraceptive (OC) Users**

In one study of 3 years of ORILISSA 150 mg once daily then completed suicide 2 days after ORILISSA discontinuation. She had no recent relevant medical history. Stress was noted.
(male and female) and liver (males only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans. Elagolix was not genotoxic or mutagenic in a battery of tests, including the in vitro bacterial reverse mutation assay, the in vitro mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the in vivo mouse micronucleus assay. In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat [see Use in Specific Populations], and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

PATIENT COUNSELING INFORMATION
Advised patients to read the FDA-approved patient labeling (Medication Guide).
• Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs [see Contraindications and Warnings and Precautions].
• There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Inform patients they can enroll by calling 1-853-762-7241 [see Use in Specific Populations].
• Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
• Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D [see Warnings and Precautions].
• Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention [see Warnings and Precautions].
• Inform patients that liver injury [see Warnings and Precautions].
• Instruct patients on signs and symptoms of liver injury [see Warnings and Precautions].
• Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as she remembers and then resume the regular dosing schedule:
  • 150 mg once daily: no more than 1 tablet each day should be taken.
  • 200 mg twice daily: no more than 2 tablets each day should be taken.

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†OBG MANAGEMENT recognizes the importance of addressing the reproductive health of gender-diverse individuals.
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EDITORIAL

9vHPV vaccine: Prevention of oropharyngeal cancer

Most clinicians and many parents know that the 9vHPV vaccine prevents cervical cancer. Less well known is that the 9vHPV vaccine was approved in 2020 to prevent oropharyngeal cancer.

Surprisingly, in the United States, the most common cancer associated with human papillomavirus (HPV) is oropharyngeal squamous cell cancer (SCC), with one study reporting 15,479 cases among men and 3,428 cases among women in 2015. In the same year, the investigators reported 11,788 cases of cervical cancer. A public health concern is that cases of oropharyngeal SCC are increasing, while cases of cervical cancer are decreasing. From 1999 to 2015, the rate of oropharyngeal SCC increased annually among both men and women, at rates of 2.7% and 0.8% per year, respectively. By contrast, the rate of cervical cancer decreased by 1.6% per year.

Although the incidence of HPV-negative oropharyngeal SCC (cases associated with cigarette smoking) has declined by 50% from 1988 to 2004, the incidence of HPV-positive oropharyngeal SCC has increased by 225%, with much of the increase occurring among young, white men.

HPV infection is a major cause of oropharyngeal SCC at the base of the tongue and tonsils, but not in the soft palate or oropharyngeal walls.

Most physicians and parents recognize that the 9-valent (9v)HPV vaccine prevents the majority of cervical cancers and precancers in women. Far fewer people realize that there is an important opportunity to prevent a large number of oropharyngeal cancers by improving 9vHPV vaccination in men and women.

Which HPV types are associated with oropharyngeal cancer?

HPV16 is the most common HPV type associated with oropharyngeal SCC. Among these cancer types, greater than 80% harbor HPV16, with greater than 90% harboring HPV16 or 18 and less than 10% of tumors associated with HPV types 31, 33, 45, 52, or 58.

The high prevalence of HPV16 in patients with oropharyngeal cancer raises the question of the HPV status of the intimate partner of the index patient. In one study of 164 people with HPV detected in their oropharyngeal, the partner of the index patient had a low prevalence of high-risk HPV types (1.2%) in oral rinse and gargle samples, similar to the rate in the general population (1.3%). This finding is reassuring and suggests that intimate partners of patients with HPV-positive oropharyngeal cancer effectively clear high-risk HPV virus from the oropharynx. The HPV status of the genital tissue of the intimate partner of an index patient with oropharyngeal SCC has not been adequately studied.

Men are more likely than women to harbor oral HPV

Among a sample of 5,501 men and women aged 14 to 69 years from the National Health and Nutrition Examination Survey, oral rinses were obtained and analyzed for the presence of HPV. The prevalence of any oral HPV and any oral high-risk HPV was 6.9% and 3.7%, respectively. Oral HPV-16 was detected in 1.6% of men and 0.3% of women. The prevalence of HPV was higher among current smokers, heavy alcohol drinkers,

CONTINUED ON PAGE 14
SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

Complications of insertion and removal

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

NEXPLANON and pregnancy

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

Educate her about the risk of serious vascular events

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

Talk to your patients about NEXPLANON — the only non-uterine LARC option

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

LARC = long-acting reversible contraceptive.
* 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)

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.
The proportion of 90-day intervals with these bleeding patterns are summarized in Table 2.

**Bleeding Patterns Definitions %†**

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>During the First 2 Years of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influent</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>%†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influent</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>

Note:* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days following insertion.

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

**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 vein thrombosis, retinal vein thrombosis, and pulmonary embolism). IMPLANON® is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of cardiovascular and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and stroke in women using etonogestrel implants. IMPLANON® should be removed in the event of a thrombosis.

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

**Ovarian Cysts**

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

**Carcinomas of the Breast and Reproductive Organs**

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

**Liver Disease**

Dyslipidemia or liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove IMPLANON if jaundice develops. Hepatic adenomas and hepatocellular carcinoma are rare with combination hormonal contraceptives use. An estimate of the attributable risk is 1.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like IMPLANON. The progestin in IMPLANON may be poorly metabolized in women with active liver disease or liver cancer is contraindicated [see Contraindications].

**Weight Gain**

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the use of IMPLANON inserts or infections may be caused by the nidation of the implant in the upper arm overlying the triceps muscle about 8-10 cm (3–4 inches) from the medial epicondyle of the humerus and 3–5 cm (1.25–2 inches) posterior to the humerus (groove) between the triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subcutaneously (depth of insertion) may not be palpable and the localization and/or removal can be difficult or impossible [see Dosage and Administration and Warnings and Precautions]. PREPARATIONS must be inserted by the expiration date stated on the packaging. IMPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant should be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

**Ectopic Pregnancies**

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

**Complications of Insertion and Removal**

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

**Spots or Bleeding**

0 Days 19% 24% 17%

19-30 Days 21% 24% 18%

31-60 Days 20% 23% 15%

61-90 Days 20% 24% 15%

91-180 Days 23% 26% 16%

**Non-Radiopaque Etonogestrel Implant (IMPLANON)**

• Allergic reaction to any of the components of NEXPLANON [see Adverse Reactions]

**Warnings and Precautions**

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

**Complications of Insertion and Removal**

IMPLANON® should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert IMPLANON® properly may go undetected immediately after insertion. A palpable implant inserted in the correct location may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paroxysmal bleeding, hematoma formation, or infection, may occur.

If IMPLANON® is inserted intramurally (in the perivascular fascia), there is a potential for the implant to be palpable, which could lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paroxysmal bleeding, hematoma formation, or infection, may occur.

If IMPLANON® is inserted intramurally (in the perivascular fascia), there is a potential for the implant to be palpable, which could lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paroxysmal bleeding, hematoma formation, or infection, may occur.

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in serum were similar to those measured in patients who received the radiopaque implant (NEXPLANON). In general, the etonogestrel levels decreased rapidly following the end of treatment. 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 on the radiopaque implant), IMPLANON was as safe as the radiopaque implant. In a 2-year carcinogenicity study in mice with subcutaneous implants releasing 10 mcg etonogestrel per day (equal to approximately 5 times the systemic steady state exposure in women on the radiopaque implant), IMPLANON was as safe as the radiopaque implant.

In a 1-year carcinogenicity study in mice with subcutaneous implants releasing 10 mcg etonogestrel per day (equal to approximately 2.5 times the systemic steady state exposure in women on the radiopaque implant), IMPLANON was as safe as the radiopaque implant.
Fluid Retention

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

Contact Lenses

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

In Situ Broken or Bent Implant

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

Monitoring

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

Drug-Laboratory Test Interactions

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

ADVERSE REACTIONS

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding irregularity*</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>1.9%</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-radiopaque etonogestrel clinical trials are listed in Table 4.

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

<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>Lumbosacral pain</td>
<td>9.6%</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7.6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.2%</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>Hypersexuality</td>
<td>5.4%</td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

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

Effects of Other Drugs on Hormonal Contraceptives

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

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

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

For more detailed information, please read the Prescribing Information.

*USPI-MK8415-IPTX-1810r020

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9vHPV vaccine: Indications and immunization schedule

In 2020, the US Food and Drug Administration (FDA) approved the 9-valent human papillomavirus (9vHPV) vaccine for the prevention of oropharyngeal cancer. The 9vHPV vaccine contains inactive L1 capsid proteins for 9 HPV types, including types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccine stimulates the production of neutralizing antibodies to the capsid protein. 9vHPV is approved for females aged 9 to 45 years to prevent cancers and precancers of the cervix, vulva, vagina, and anus caused by HPV types 16, 18, 31, 33, 45, 52, and 58. It is also approved for males aged 9 to 45 years to prevent precancers and the anuses caused by those viral types. In 2020 the 9vHPV vaccine was approved by the FDA to prevent oropharyngeal cancer in males and females. Of note, the FDA reported that, “the oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls and boys, 11 to 12 years of age. Children with a history of sexual abuse or assault can start the vaccine at 9 years of age. Catch-up vaccination is recommended for all females and males through age 26 years. The ACIP recommends shared clinical decision-making regarding vaccination for some adults 27 to 45 years of age. Gynecologists with routine exposure to HPV may have occupational risk that warrants HPV vaccination (see “As a gynecologist, should you receive the 9vHPV vaccine?”).

For most individuals who start the vaccine series before age 15, two doses of 9vHPV vaccine are recommended, with the second dose 6 to 12 months following the first dose. For teens and adults aged 15 to 26 years, 3 doses of 9vHPV vaccine are recommended, with the second dose 1 to 2 months later and the third dose 6 months following the first dose. Immunocompromised individuals 9 to 26 years of age, including those with HIV infection, should receive 3 doses of the vaccine.

References

and people with a history of a greater number of sexual partners. In men and women reporting more than 20 lifetime sexual partners, the prevalence of oral HPV was 20%.

In a study of 2,627 men and women aged 18 to 33 years, the prevalence of oral HPV 16/18/6/11 was lower among those vaccinated versus those unvaccinated (0.11% and 1.6%, respectively; P = .008). Among men, oral HPV 16/18/6/11 was lower among those vaccinated versus unvaccinated (0.0% and 2.13%, respectively; P = .007). The results of this observational study support the important role of vaccination in reducing oral HPV infection.

Vaccinate boys and girls to prevent cancer

Most population studies report that males are less likely to receive an HPV vaccine than females. For example, based on the National Health Interview Survey of people aged 18 to 26, the percentage of women who self-reported receiving at least one dose of HPV vaccine was 37% in 2013 and 54% in 2018. By contrast, among men, the rates of self-reported vaccination were much lower—8% in 2013 and 27% in 2018.

The percentage of women who received the recommended number of doses of HPV vaccine (see “9vHPV vaccine: Indications and immunization schedule”) was 26% in 2013 and 35% in 2018. For men, these percentages were 2% in 2013 and 9% in 2018. These data indicate that, compared with women, men are less likely to receive an HPV vaccination and far less likely to have received the recommended number of doses. It is heartening that there has been a slow and steady increase in the prevalence of HPV vaccination. In fact, increasing the HPV vaccination rate among both boys and girls has the potential to markedly reduce the incidence of oropharyngeal cancer.

The reasons for the female-male gap in vaccination rates are not fully characterized. For one, parental awareness of the importance of HPV vaccination to prevent cancer among men is limited, and represents an important opportunity for additional public health education. In a qualitative interview study of mothers with children aged 11 to 19, the investigators reported that most mothers were aware that HPV vaccination could prevent cervical cancer in women, but most mothers did not know that HPV causes cancer of the mouth and that vaccination could prevent oropharyngeal cancer in boys and girls. Because of this lack of knowledge,
As a gynecologist, should you receive the 9vHPV vaccine?

Surgical treatment of tissues infected with human papillomavirus (HPV) often involves the use of laser or electrosurgical devices that generate smoke, which is known to contain HPV nucleic acid sequences and may contain infective virions. It is known that HPV nucleic acid sequences are present in surgical smoke. In one study plantar warts were treated with a carbon dioxide laser or electrocoagulation. The vapor produced from the surgery was collected with a dry filter apparatus. Five of 8 laser-derived vapors and 4 of 7 electrocoagulation-derived vapors were positive for HPV DNA. The concentration of HPV DNA was greater with laser than with electrocoagulation treatment.

It is not known if surgical smoke derived from treatment of HPV-infected tissues contains infective HPV virions. In an experimental bovine model, smoke generated by laser ablation of fibropapillomas was collected. Injection of the contents of the smoke caused cutaneous papillomavirus lesions when inoculated into calves, suggesting that the smoke contained infective HPV virions. Although this animal experiment is a proof of principle that surgical smoke generated from treatment of HPV-infected tissue contain virions, it is unclear if surgical smoke generated in gynecologic practice contains HPV virions.

To investigate the prevalence of nasal HPV DNA among gynecologists, 700 physicians in Zhejiang Province, China, completed a questionnaire and provided a nasal swab for HPV DNA analysis. Among gynecologists who performed or did not perform LEEP, the prevalence of HPV DNA in the nose was 10% and 3%, respectively. The most common HPV types detected were HPV16 (76%), HPV31 (10%), HPV58 (5%), HPV55 (5%), HPV56 (2%), and HPV59 (2%). Among gynecologists who performed LEEP procedures, the prevalence of HPV DNA was 19% for those who did not use a surgical mask, 8% for clinicians who used a standard surgical mask, and 0% for those who used an N95 filtering facepiece respirator, suggesting that an N95 respirator provides the greatest protection from surgical smoke. Over 24 months of follow-up, all the gynecologists who had initially tested positive for HPV DNA no longer had detectable nasal HPV DNA. In this study, no gynecologist was diagnosed with an HPV-associated oropharyngeal disease. The investigators concluded that surgical masks, especially an N95 respirator, should be used by gynecologists performing LEEP procedures.

Investigators also have evaluated for the presence of HPV DNA in matched samples from the cervix of 134 patients undergoing loop electrosurgical excision procedure (LEEP) for cervical dysplasia, as well as the smoke generated during the procedure and nasal swabs from the surgeon performing the LEEP. HPV DNA was detected in 95% of the cervical samples, 30% of the surgical smoke samples, and 1.5% of the surgeons’ nasal swabs. At 6 months of follow-up, the two surgeons who initially had HPV-positive nasal swabs no longer had detected HPV DNA.

Of concern is that otolaryngologists have reported sporadic cases of oropharyngeal squamous cell cancer and laryngeal papillomatosis in health care workers with frequent and repetitive exposure to HPVs. For example, in one case report, a 53-year-old male gynecologist, nonsmoker, presented to his physician with a lump on the neck. The gynecologist had a 53-year-old male gynecologist, nonsmoker, presented to his physician with a lump on the neck. The gynecologist had 35 fractions of radiotherapy and adjuvant cisplatin. Treatment adverse effects included dysphagia and xerostomia, and the patient lost 40 pounds.

Available interventions to reduce exposure of clinicians to HPV virions that may be present in surgical smoke include:
• wearing a fit-tested N95 respirator
• routinely using a smoke evacuation device, and
• ensuring sufficient ventilation in the procedure room.

A new recommendation is to consider 9vHPV vaccination for clinicians who are routinely exposed to HPV virions.

In February 2020, the American Society for Colposcopy and Cervical Pathology recommended that clinicians who are routinely exposed to HPV consider 9vHPV vaccination. This recommendation pertains to all members of the clinical team in the procedure room, including physicians, nurses, and staff. Based on the available data, gynecologists who have not been vaccinated will need to weigh the benefits and costs of receiving a 9vHPV vaccine to protect themselves against an occupational exposure that may adversely impact their health.

References
the mothers did not think their sons needed to have an HPV vaccine. The research report is aptly titled, “I don’t think he needs the HPV vaccine cause boys can’t have cervical cancer.”

Clinicians are highly influential in guiding parents to accept HPV vaccination of their children. Offering consistent messaging to parents that HPV vaccination prevents cancer in both women and men, and reducing the out-of-pocket cost of vaccination surely will result in an increase in the vaccination rate of boys and girls. ●

References

SGS video series!

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Brought to you by the Society of Gynecologic Surgeons

Safety and efficiency in the laparoscopic hysterectomy: Techniques to optimize the surgical approach

JACOB LAUER, MD, MPH; ARNOLD ADVINCUALA, MD; JIN HEE KIM, MD

In this video, the authors highlight surgical techniques that can be used to improve the safety and efficiency of the laparoscopic hysterectomy. During separation of the adnexa, preserving the orientation of the round ligament, IP, and pelvic sidewall allows the ovary to remain in its anatomic location. Generous dissection of the vesicouterine reflection permits a safe closure of the cuff. Lateralization of the uterine vascular pedicle prevents bleeding and protects the ureter. Angled suturing in the cuff provides for hemostatic closure.

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Which hormonal management approach for women with premature ovarian insufficiency is best for bone?

The use of combined oral contraceptives (COCs) in 119 women with a mean age of 30.3 years who had premature ovarian insufficiency was associated with the most positive trends in bone mineral density (BMD). Bone density scans revealed that women who used COC or high-dose estrogen plus progesterone therapy (EPT) had increases in BMD at the lumbar spine, while women who used no treatment or low-dose EPT experienced declines in lumbar spine BMD.


EXPERT COMMENTARY
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Premature ovarian insufficiency (POI) refers to a condition in women in whom ovarian function ceases prior to age 40 years. Although hormone therapy (HT) is a mainstay of treatment for women with POI, it is uncertain which approach to HT is most effective in terms of bone mineral density (BMD). Investigators recently published their results of an observational study that aimed to evaluate the use of combined oral contraceptives (COCs) for preserving BMD in women with POI.

Details of the study
At an academic center in Brazil, Carvalho Gazarra and colleagues identified women with POI who had undergone 2 or more BMD assessments performed 2 or more years apart.1 HT regimens (all of which were taken continuously) employed the following: a COC with ethinyl estradiol (EE) 30 µg and levonorgestrel; low-dose estrogen plus progestin therapy (EPT, conjugated equine estrogen [CEE] 0.625 mg with medroxyprogesterone acetate or estradiol 1.0 mg with norethindrone acetate); or high-dose estrogen plus progestin (CEE 1.25 mg or estradiol 2.0 mg combined with the same progestins).

Results. Among 119 evaluable women with POI (mean age, 30.3 years), the use of COC was associated with the most positive BMD trends. For women using COC or high-dose EPT, BMD at the lumbar spine increased. By contrast, BMD of the lumbar spine declined

The author reports serving on the advisory boards of Pfizer (contraception) and Mithra, and that the University of Florida has received clinical trial support from Mithra.

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Examining the EVIDENCE

WHAT THIS EVIDENCE MEANS FOR PRACTICE

When replacing estrogen and progestin in young women who lack ovarian function, it is appropriate to use considerably higher doses than those used to treat bothersome vasomotor symptoms in women with normal/spontaneous menopause. From the perspective of venous thromboembolism risk, the transdermal route of administration is safer than the oral route, and the Scottish and US studies discussed here indicate that transdermal estradiol is an effective approach to maintaining skeletal health in young women without ovarian function. Accordingly, hormonal management with high-dose transdermal estradiol with a progestin (such as progesterone 200–300 mg at bedtime or medroxyprogesterone 5–10 mg daily) represents an appropriate strategy. In situations where transdermal estradiol plus oral progestin treatment is not covered by health insurance or acceptable to the patient, an oral estrogen-progestin contraceptive formulated with EE 30 or 35 µg will provide protection against bone loss.

References

Coming soon...

- Break this practice habit: Routine preoperative testing
  Kimberly Kho, MD

- Using pessaries for POP and urinary stress incontinence
  Henry Lerner, MD

- Home pregnancy tests—Is ectopic pregnancy always on your mind?
  Joseph S. Sanfilippo, MD, and Steven R. Smith, MS, JD

- For obese postmenopausal women, what options are available to decrease their risk of developing endometrial cancer?
  Robert L. Barbieri, MD

- ID consult: Bacterial vaginosis
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**References:**
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Syphilis: Cutting risk through primary prevention and prenatal screening

This highly infectious STI poses severe consequences to women and babies when infection occurs during pregnancy, with infection rates higher among women who lack prenatal care. These authors stress education of at-risk populations and early recognition of clinical features to quell rising infection rates.

Tory A. Finley, BA, and Patrick Duff, MD

CASE  Pregnant woman with positive Treponema pallidum antibody test
A 30-year-old primigavida at 10 weeks and 4 days of gestation by her last menstrual period presents to your office for her initial prenatal visit. She expresses no concerns. You order the standard set of laboratory tests, including a sexually transmitted infection (STI) screening panel. Consistent with your institution’s use of the reverse algorithm for syphilis screening, you obtain a Treponema pallidum antibody test, which reflexes to the rapid plasma reagin (RPR) test. Three days later, you receive a notification that this patient’s T pallidum antibody result was positive, followed by negative RPR test results. The follow-up T pallidum particle agglutination (TP-PA) test also was negative. Given these findings, you consider:

- What is the correct interpretation of the patient’s sequence of test results?
- Is she infected, and does she require treatment?

Meet our perpetrator
Syphilis has plagued society since the late 15th century, although its causative agent, the spirochete T pallidum, was not recognized until 1905. T pallidum bacteria are transmitted via sexual contact, as well as through vertical transmission during pregnancy or delivery. Infection with syphilis is reported in 50% to 60% of sexual partners after a single exposure to an infected individual with early syphilis, and the mean incubation period is 21 days. T pallidum can cross the placenta and infect a fetus as early as the sixth week of gestation. Congenital syphilis infections occur in the neonates of 50% to 80% of women with untreated primary, secondary, or early latent syphilis infections; maternal syphilis is associated with a 21% increased risk of stillbirth, a 6% increased risk of preterm delivery, and a 9% increased risk of neonatal death. Additionally, syphilis infection is associated with a high risk of HIV infection, as well as coinfection with other STIs.

Given the highly infective nature of T pallidum, as well as the severity of the potential consequences of infection for both mothers and babies, primary prevention,
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education of at-risk populations, and early recognition of clinical features of syphilis infection are of utmost importance in preventing morbidity and mortality. In this article, we review the epidemiology and extensive clinical manifestations of syphilis, as well as current screening recommendations and treatment for pregnant women.

**The extent of the problem today**

Although US rates of syphilis have ebbed and flowed for the past several decades, the current incidence has grown exponentially in recent years, with the number of cases reported to the Centers for Disease Control and Prevention (CDC) increasing by 71% from 2014 to 2018. During this time period, reported cases of primary and secondary syphilis in women more than doubled (172.7% and 165.4%, respectively) according to CDC data, accompanied by a parallel rise in reported cases of congenital syphilis in both live and stillborn infants. In 2018, the CDC reported a national rate of congenital syphilis of 33.1 cases per 100,000 live births, a 39.7% rise compared with data from 2017.

**Those most at risk.** Risk factors for syphilis infection include age younger than 30 years, low socioeconomic status, substance abuse, HIV infection, concurrent STIs, and high-risk sexual activity (sex with multiple high-risk partners). Additionally, reported rates of primary and secondary syphilis infections, as well as congenital syphilis infections, are more elevated among women who identify as Black, American Indian/Alaska Native, and/or Hispanic. Congenital infections in the United States are correlated with a lack of prenatal care, which has been similarly linked with racial and socioeconomic disparities, as well as with untreated mental health and substance use disorders and recent immigration to the United States.

**The many phases of syphilis**

The characteristic lesion of primary syphilis is a chancre, which is a painless, ulcerative lesion with raised borders and a clean, indurated base appearing at the site of spirochete entry (FIGURE 1). Chancre most commonly appear in the genital area, with the most frequent sites in females being within the vaginal canal or on the cervix. Primary chancre tend to heal spontaneously within 3 to 6 weeks, even without treatment, and frequently are accompanied by painless inguinal lymphadenopathy. Given that the most common chancre sites are not immediately
apparent, primary infections in women often go undetected.\textsuperscript{3} In fact, it is essential for clinicians to recognize that, in our routine practice, most patients with syphilis will not be symptomatic at all, and the diagnosis will only be made by serologic screening.

Following resolution of the primary phase, the patient may enter the secondary stage of \textit{T. pallidum} infection. During this stage, spirochetes may disseminate throughout the bloodstream to infect all major organ systems. The principal manifestations of secondary syphilis include a diffuse maculopapular rash that begins on the trunk and proximal extremities and spreads to include the palms and soles (\textbf{FIGURE 2}); mucosal lesions, such as mucous patches and condyloma lata (\textbf{FIGURE 3}); nonscarring alopecia; periostitis; generalized lymphadenopathy; and, in some cases, hepatitis or nephritis.\textsuperscript{1,3}

Secondary syphilis usually clears within 2 to 6 weeks, with the patient then entering the early latent stage of syphilis. During this period, up to 25\% of patients are subject to flares of secondary syphilitic lesions but otherwise are asymptomatic.\textsuperscript{1,3,4} These recurrences tend to occur within 1 year, hence the distinction between early and late latent stages. Once a year has passed, patients are not contagious by sexual transmission and are unlikely to suffer a relapse of secondary symptoms.\textsuperscript{1,3} However, late latent syphilis is characterized by periods of intermittent bacteremia that allow for seeding of the placenta and infection in about 10\% of fetuses.\textsuperscript{5}

Untreated, about 40\% of patients will progress to the tertiary stage of syphilis, which is characterized by gummas affecting the skin and mucous membranes (\textbf{FIGURE 4}) and cardiovascular manifestations including arterial aneurysms and aortic insufficiency.\textsuperscript{3}

Neurologic manifestations of syphilis may arise during any of the above stages, though the most characteristic manifestations tend to appear decades after the primary infection. Early neurosyphilis may present as meningitis, with or without concomitant ocular syphilis (uveitis, retinitis) and/or as otic syphilis (hearing loss, persistent tinnitus).\textsuperscript{1,5} Patients with late (tertiary)
neurosyphilis tend to exhibit meningo-vascular symptoms similar to stroke (aphasia, hemiplegia, seizures) and/or parenchymal effects such as general paresis. Tabes dorsalis (manifestations of which include urinary and rectal incontinence, lightning pains, and ataxia) is a late-onset manifestation.1,3

Congenital syphilis can be subdivided into an early and late stage. The first stage, in which clinical findings occur within the first 2 years of life, commonly features a desquamating rash, hepatomegaly, and rhinitis. Anemia, thrombocytopenia, periostitis, and osteomyelitis also have been documented.5

Of note, two-thirds of infants are asymptomatic at birth and may not develop such clinical manifestations for 3 to 8 weeks.3 If untreated, early congenital infection may progress to late manifestations, such as Hutchinson teeth, mulberry molars, interstitial keratitis, deafness, saddle nose, saber shins, and such neurologic abnormalities as developmental delay and general paresis.3

Prenatal screening and diagnosis

Current recommendations issued by the CDC and the American College of Obstetricians and Gynecologists state that all pregnant women should be screened for syphilis infection at their first presentation to care, with repeat screening between 28 and 32 weeks of gestation and at birth, for women living in areas with a high prevalence of syphilis and/or with any of the aforementioned risk factors.3,5 Given that providers may be unfamiliar with the prevalence of syphilis...
in their area, and that patients may acquire or develop an infection later on in their pregnancy, researchers have begun to investigate the feasibility of universal third-trimester screening. While the cost-effectiveness of such a protocol is disputed, recent studies suggest that it may result in a substantial decrease in adverse maternal and fetal outcomes.8,9

**Diagnostic tests**

The traditional algorithm for the diagnosis of syphilis infection begins with a nontreponemal screening test, such as the RPR or the Venereal Disease Research Laboratory test. If positive, these screening tests are followed by a confirmatory treponemal test, such as the fluorescent treponemal antibody (FTA) test or the TP-PA (FIGURE 5).

The “reverse” screening algorithm begins with the FTA and, if positive, reflexes to the RPR. A reactive RPR indicates an active infection, and the patient should be treated. A negative RPR should be followed by the TP-PA to rule out a false-positive immunoglobulin G test. If the TP-PA test result is positive, the diagnosis of syphilis is confirmed (FIGURE 6). It is crucial to understand, however, that treponemal antibodies will remain positive for a patient’s lifetime, and someone who may have been treated for syphilis in the past also will screen positive. Once 2
Treponemal tests are positive, physicians should take a careful history to assess prior infection risk and treatment status. A negative TP-PA excludes a diagnosis of syphilis.

**Advantages of the reverse screening algorithm.** Nontreponemal tests are inexpensive and easy to perform, and titers allow for identification of a baseline to evaluate response to treatment. However, given the fluctuation of RPR sensitivity (depending on stage of disease and a decreased ability to detect primary and latent stages of syphilis), there has been a resurgence of interest in the reverse algorithm. While reverse screening has been found to incur higher costs, and may result in overtreatment and increased stress due to false-positive results, there is evidence to suggest that this algorithm is more sensitive for primary and latent infections.

Given the rise in prevalence of syphilis infections in the United States over the past decade, and therefore a higher pretest probability of syphilis in the population, we favor the reverse screening algorithm in obstetrics, particularly given the risks of adverse maternal and fetal outcomes.

**Treating syphilis in pregnancy**

Parenteral benzathine penicillin G is the only currently recommended medication for the treatment of syphilis in pregnancy. This drug is effective in treating maternal infection and in preventing fetal infections, as well as in

### TABLE  Common presentations and treatment of syphilis in pregnancy

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Characteristic manifestation</th>
<th>Treatment regimen</th>
</tr>
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<tbody>
<tr>
<td>Primary</td>
<td>Chancre</td>
<td>Benzathine penicillin G, 2.4 million units IM in a single dose*</td>
</tr>
</tbody>
</table>
| Secondary        | • Diffuse maculopapular rash that includes the palms and soles  
|                  | • Condyloma lata             | Benzathine penicillin G, 2.4 million units IM in a single dose* |
|                  | • Mucous patches             |                   |
|                  | • Alopecia                   |                   |
| Early latent (<1 y) | No characteristic lesion; patients may experience recurrence of secondary symptoms | Benzathine penicillin G, 2.4 million units IM in a single dose* |
| Late latent (>1 y) | No cutaneous lesions         | Benzathine penicillin G, 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1-week intervals |
| Tertiary         | Gummas                       | Benzathine penicillin G, 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1-week intervals |
| Confirmed neurosyphilis | • Argyll-Robertson pupil  
|                  | • Tabes dorsalis             | Aqueous crystalline penicillin G, 18-24 million units/d, administered as 3-4 million units IV every 4 hours or by continuous infusion for 10-14 days  
|                  | • CVA                        | OR Procaine penicillin, 2.4 million units IM/day, plus probenecid 500 mg orally every day, both for 10-14 days |
|                  | • General paresis            |                   |
|                  | • Dementia                   |                   |

*Based on reports of failure to prevent congenital syphilis in women with primary, secondary, or early latent syphilis, despite adherence to treatment guidelines, some experts advocate for a second dose of 2.4 million units of benzathine penicillin G no later than 10 days after the first injection.

**Abbreviations:** CVA, cerebrovascular accident; IM, intramuscular; IV, intravenous.
treating established fetal infections. Regimens differ depending on the stage of syphilis infection (TABLE). Treatment for presumed early syphilis is recommended for women who have had sexual contact with a partner diagnosed with primary, secondary, or early latent syphilis within 3 months of their current pregnancy. Any patient with diagnosed syphilis who demonstrates clinical signs of neurologic involvement should undergo lumbar puncture to assess for evidence of neurosyphilis. CDC guidelines recommend that patients who report an allergy to penicillin undergo desensitization therapy in a controlled setting, as other antibiotics that have been investigated in the treatment of syphilis are either not appropriate due to teratogenicity or due to suboptimal fetal treatment.

Syphilotherapy may lead to the Jarisch-Herxheimer reaction, which is an acute systemic reaction to inflammatory cytokines produced in response to lipopolysaccharide released by dying spirochetes. This reaction is characterized by fever, chills, myalgia, headache, hypotension, and worsening of cutaneous lesions. Preterm labor and delivery and fetal heart rate tracing abnormalities also have been documented in pregnant women experiencing this reaction, particularly during the second half of pregnancy. Prior to the start of treatment, a detailed sonographic assessment should be performed to assess the fetus for signs of early syphilis, including hepatomegaly, elevated peak systolic velocity of the middle cerebral artery (indicative of fetal anemia), polyhydramnios, placentalomegaly, or hydrops.

**CASE Resolved**
The combination of the patient’s test results—positive FTA, negative RPR, and negative TP-PA—suggest a false-positive treponemal assay. This sequence of tests excludes a diagnosis of syphilis; therefore, no treatment is necessary. Depending on the prevalence of syphilis in the patient’s geographic location, as well as her sexual history, rescreening between 28 and 32 weeks may be warranted.

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CASE Heart rate tracing suggests fetal distress
Ms. M. presents for elective induction of labor at 39 weeks’ gestation. During the course of her labor, a Category II fetal heart rate (FHR) tracing is noted, and maternal oxygen is administered as part of the intrauterine resuscitative efforts. Her infant ultimately was delivered vaginally with an arterial cord blood pH of 7.1 and Apgar scores of 5 and 7.

Should intrauterine resuscitation include maternal oxygen administration?

It is a common sight on labor and delivery: An FHR monitoring strip is noted to be a Category II tracing. There may be fetal tachycardia, late decelerations, or perhaps decreased variability. The nurse or physician goes to the laboring mother’s room, checks cervical dilation, changes the patient’s position, and puts an oxygen mask over her face.

The American College of Obstetricians and Gynecologists (ACOG) lists maternal oxygen administration, most commonly at 10 L/min via a nonrebreather face mask, as an intrauterine resuscitative measure for Category II or Category III FHR tracings. Maternal oxygen is used to treat abnormal FHR tracings in approximately half of all births in the United States. Despite these recommendations and the frequency of its use, however, evidence is limited that maternal oxygenation improves neonatal outcome. In fact, there is emerging evidence of potential harm.

Why use oxygen?
The use of maternal oxygen supplementation intuitively makes sense. We know that certain abnormalities in FHR tracings can signal fetal hypoxia. Left untreated, the hypoxia could lead to fetal acidemia and associated neonatal sequelae. Theoretically, the administration of maternal oxygen should lead to improved fetal oxygenation and improved fetal outcome. This is supported by studies from the 1960s that demonstrate improved FHR tracings after maternal oxygen administration.

This idea was further supported by studies that demonstrated an increase in fetal oxygen levels when maternal oxygen is administered. Haydon and colleagues evaluated the administration of maternal oxygen in women with nonreassuring FHR tracings. Their data showed that maternal oxygen...
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administration increased fetal oxygen as measured by fetal pulse oximetry. The lower the initial fetal oxygen levels prior to oxygen administration, the greater the increase.

Despite these findings, evidence for improved neonatal outcomes is lacking. While heart rate tracings and fetal oxygen saturation may be improved with maternal oxygen supplementation, neonatal morbidity appears to remain unchanged (FIGURE). In fact, newer research suggests potential harm. Although an improved FHR tracing may be comforting to the clinician, the end result may be less so. Given these findings on maternal oxygen supplementation, it is time to break this practice habit.

**Maternal cardiovascular effects**

Most of the literature on maternal hyperoxegenation focuses on fetal response. Before examining the effects on the fetus, however, we must consider the effect on the mother. Cardiovascular changes occur during and after maternal oxygen administration that should be taken into account.

McHugh and colleagues measured the hemodynamic changes in 46 pregnant and 20 nonpregnant women before, immediately, and 10 minutes after a 30-minute period of high-flow oxygen administration. While there were no changes in the nonpregnant women’s parameters, in the pregnant women heart rate and stroke volume were decreased after oxygen administration. Additionally, systemic vascular resistance increased and did not return to baseline by 10 minutes postadministration.

Since the purpose of the maternal oxygen administration is to increase oxygen to the fetus, this decrease in cardiac output and increase in systemic vascular resistance is concerning. These results may negate the intended effect of increased oxygen delivery to the fetus.

**Maternal and fetal oxidative stress**

Assuming that the abnormal FHR tracing in our case patient is actually due to fetal hypoxia, it would seem prudent to increase fetal oxygenation. However, fetal hyperoxegenation may lead to free radical damage that could worsen neonatal outcomes. Oxidative stress, which can be caused by both hypoxia and hyperoxia, can lead to endothelial and cell receptor damage. This is known to contribute to the cerebral damage of hypoxic-ischemic encephalopathy.

In a randomized trial, Khaw and colleagues measured lipid peroxidases as a “free radical footprint” in women undergoing elective cesarean delivery who were administered oxygen or room air. Maternal and fetal oxygen levels were higher in the oxygen-supplementation group, but lipid peroxidases also were elevated. This finding suggests that the excess oxygen results in free radical formation and potentially negative effects on the neonate.

Although maternal oxygen supplementation frequently is viewed as harmless, this research shows that free radical damage may occur in the mother as well.

Additional research shows that longer durations of oxygen administration are correlated with worsening neonatal outcomes. In a study of liberal versus indicated oxygen use, the average time was approximately 90 minutes. Use for longer than 176 minutes was associated with lower oxygen levels in fetal blood. A proposed mechanism for this response is placental vasoconstriction thought to protect the fetus from free radical damage.

Again, if the goal is to increase oxygenation, prolonged maternal oxygen supplementation appears to produce the opposite effect.

**Fetal acidemia and neonatal morbidity**

If a fetus with an abnormal FHR tracing is thought to be hypoxic or acidic, adding
the potentially harmful effects of free radicals could worsen this condition. This is exactly what Raghuraman and colleagues demonstrated in a large prospective cohort analysis.\(^9\) While there was no difference in neonatal morbidity between those receiving oxygen and those on room air, there was a significant difference among infants with acidemia and hyperoxia. Composite morbidity (mechanical ventilation, hypothermic therapy, meconium aspiration, and death) was significantly increased in neonates with both hyperoxia and acidemia compared with nonacidemic hyperoxic infants.\(^9\) This is further supported by reports of an increased need for neonatal resuscitation and a fourfold increase in umbilical cord pH of less than 7.2.\(^10\)

While intrauterine and extrauterine life certainly differ, these findings align with the pediatric literature that supports neonatal resuscitation with room air rather than 100% oxygen.\(^11\) Additionally, the intrauterine environment is relatively hypoxic, which may make free radical damage more severe.

### Oxygen use during the COVID-19 pandemic

While high-flow oxygen by mask is not considered an aerosol-generating procedure according to the Centers for Disease Control and Prevention, data are limited regarding the cleaning and filtering of oxygen. It is unknown if high-flow oxygen by mask increases the risk of infectious disease transmission to care providers. Therefore, in the midst of the COVID-19 pandemic, ACOG currently recommends against using supplemental oxygen for Category II and Category III tracings, since the benefits are not well established and the possibility of harm to providers may be increased.\(^12\) Oxygen supplementation still should be used in mothers with hypoxia.

### Other intrauterine resuscitation options

Maternal oxygen administration does not appear beneficial for neonatal outcomes, but other methods can be used. An intravenous fluid bolus and lateral positioning of the mother, for example, are both associated with increased fetal oxygenation. Reducing uterine activity by discontinuing oxytocin or cervical ripening agents or by administering a tocolytic also can improve FHR abnormalities. Oxygen use should be reserved for patients with maternal hypoxia.

### The bottom line

The liberal use of maternal oxygenation for the management of abnormal FHR tracings should be stopped. Clear evidence of its benefit is lacking, and the real possibility of fetal and maternal harm remains. This may be especially true during the COVID-19 pandemic.

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**References**

Unrecognized placenta accreta spectrum: Intraoperative management

Assembling a multidisciplinary team and preparing for massive bleeding are essential components of the surgical plan for managing PAS.

Charlotte Gamble, MD, MPH, and Fady Khoury-Collado, MD

CASE Concerning finding on repeat CD
A 30-year-old woman with a history of 1 prior cesarean delivery (CD) presents to labor and delivery at 38 weeks of gestation with symptoms of mild cramping. Her prenatal care was uncomplicated. The covering team made a decision to proceed with a repeat CD. A Pfannenstiel incision is made to enter the abdomen, and inspection of the lower uterine segment is concerning for a placenta accreta spectrum (PAS) (FIGURE, page 34).

What would be your next steps?

Placenta accreta spectrum describes the range of disorders of placental implantation, including placenta accreta, increta, and percreta. PAS is a significant cause of severe maternal morbidity and mortality, primarily due to massive hemorrhage at the time of delivery. The incidence of PAS continues to rise along with the CD rate. The authors of a recent meta-analysis reported a pooled prevalence rate of 1 in 588 women. Notably, in women with PAS, the rate of hysterectomy is 52.2%, and the transfusion-dependent hemorrhage rate is 46.9%.

Ideally, PAS should be diagnosed or at least suspected antenatally during prenatal ultrasonography, leading to delivery planning by a multidisciplinary team. The presence of a multidisciplinary team—in addition to the primary obstetric and surgical teams—composed of experienced anesthesiologists, a blood bank able to respond to massive transfusion needs, critical care specialists, and interventional radiologists is associated with improved outcomes.

Occasionally, a patient is found to have an advanced PAS (increta or percreta) at the time of delivery. In these situations, it is paramount that the appropriate resources be assembled as expeditiously as possible to optimize maternal outcomes. Surgical management can be challenging even for experienced pelvic surgeons, and appropriate resuscitation cannot be provided by a single anesthesiologist working alone. A cavalier attitude of proceeding with the delivery “as usual” in the face of an unexpected PAS situation can lead to disastrous consequences, including maternal death.

In this article, we review the important steps to take when faced with the unexpected situation of a PAS at the time of CD.
Stop and collect your multidisciplinary team

Once the diagnosis of an advanced PAS is suspected, the first step is to stop and request the presence of your institution’s multidisciplinary surgical team. This team typically includes a maternal-fetal specialist or, if not available, an experienced obstetrician, and an expert pelvic surgeon, which varies by institution (gynecologic oncologist, trauma surgeon, urologist, urogynecologist, vascular surgeon). An interventional radiology team is an additional useful resource that can assist with the control of pelvic hemorrhage using embolization techniques.

In our opinion, it is not appropriate to have a surgical backup team available only as needed at a certain distance from the hospital or even in the building. Because of the acuity and magnitude of bleeding that can occur in a short time, the most appropriate approach is to have your surgical team scrubbed and ready to assist or take over the procedure immediately if indicated.

Additional support staff also may be required. A single circulating nurse may not be sufficient, and available nursing staff may need to be called. The surgical technician scrubbed on the case may be familiar only with uncomplicated CDs and can be
Unrecognized placenta accreta spectrum: Intraoperative management

Prepare for resuscitation

While you are calling your multidisciplinary team members, implement plans for resuscitation by notifying the anesthesiologist about the PAS findings. This will allow the gathering of needed resources that may include calling on additional anesthesiologists with experience in high-risk obstetrics, trauma, or critical care.

Placing large-bore intravenous lines or a central line to allow rapid transfusion is essential. Strongly consider inserting an arterial line for hemodynamic monitoring and intraoperative blood draws to monitor blood loss, blood gases, electrolytes, and coagulation parameters, which can guide resuscitative efforts and replacement therapies.

Simultaneously, inform the blood bank to prepare blood and blood products for possible activation of a massive transfusion protocol. It is imperative to have the products available in the operating room (OR) prior to proceeding with the surgery. Our current practice is to have 10 units of packed red blood cells and fresh frozen plasma available in the OR for all our prenatally diagnosed electively planned PAS cases.

Optimize exposure of the surgical field

Appropriate exposure of the surgical field is essential and should include exposure of the uterine fundus and the pelvic sidewalls. The uterine incision should avoid the placenta; typically it is placed at the level of the uterine fundus. Exposure of the pelvic sidewalls is needed to open the retroperitoneum and identify the ureter and the iliac vessels.

Vertical extension of the fascial incision probably will be needed to achieve appropriate exposure. Although at times this can be done without a concomitant vertical skin incision, often an inverted T incision is required. Be mindful that PAS is a life-threatening condition and that aesthetics are not a priority. After extending the fascial incision, adequate exposure can be achieved with any of the commonly used retractors or wound protectors (depending on institutional availability and surgeon preference) or by the surgical assistants using body wall retractors.

We routinely place the patient in lithotomy position. This allows us to monitor for vaginal bleeding (often a site of unrecognized massive hemorrhage) during the surgery, facilitate retrograde bladder filling, and provide a vaginal access to the pelvis. In addition, the lithotomy position allows for cystoscopy and placement of ureteral stents, which can be performed before starting the surgery to help prevent urinary tract injuries or at the end of the procedure in case one is suspected.

overwhelmed during a PAS case. Having a more experienced surgical technologist can optimize the availability of the appropriate instruments for the surgical team.

If a multidisciplinary surgical team with PAS management expertise is not available at your institution and the patient is stable, it is appropriate to consider transferring her to the nearest center that can meet the high-risk needs of this situation.

If a multidisciplinary surgical team with PAS management expertise is not available and the patient is stable, consider transferring her to the nearest center that can meet the high-risk needs of this situation.

FAST TRACK

If a multidisciplinary surgical team with PAS management expertise is not available and the patient is stable, consider transferring her to the nearest center that can meet the high-risk needs of this situation.

FIGURE Lower uterine segment suspicious for placenta accreta spectrum

Red arrow: placenta/lower uterine segment. Yellow arrow: bladder.
Performing the hysterectomy
A complete review of all surgical techniques for managing PAS is beyond the scope of this article. However, we briefly cover important procedural steps and offer suggestions on how to minimize the risk of bleeding.

In our experience. The areas with the highest risk of massive bleeding that can be difficult to control include the pelvic sidewall when there is lateral extension of the PAS, the vesicouterine space, and placenta previa vaginally. Be mindful of these areas at risk and have a plan in place in case of bleeding.

Uterine incision
Avoid the placenta when making the uterine incision, which is typically done in the fundal part of the uterus. Cut and tie the cord and return it to the uterine cavity. Close the incision in a single layer. Use of a surgical stapler can be used for the hysterotomy and can decrease the amount of blood loss.8

Superior attachments of the uterus
The superior attachments of the uterus include the round ligament, the utero-ovarian ligament, and the fallopian tubes. With meticulous dissection, develop an avascular space underneath these structures and, in turn, individually divide and suture ligate; this is typically achieved with minimal blood loss.

In addition, isolate the engorged veins of the broad ligament and divide them in a similar fashion.

In our experience. Use of a vessel-sealing device can facilitate division of all the former structures. Simply excise the fallopian tubes with the vessel-sealing device either at this time or after the uterus is removed.

Pelvic sidewall
Once the superior attachments of the uterus have been divided, the next step involves exposing the pelvic sidewall structures, that is, the ureter and the pelvic vessels. Expose the ureter from the pelvic brim to the level of the uterine artery. The hypogastric artery is exposed as well in this process and the pararectal space developed.

Steps in managing a cesarean delivery with placenta accreta spectrum
1. Stop and collect your multidisciplinary team. If required resources are not available at your institution and the patient is stable, consider transferring her to the nearest center of expertise
2. Prepare for resuscitation: Have blood products available in the operating room and optimize IV access and arterial line
3. Optimize exposure of the surgical field: place in lithotomy position, extend fascial incision, perform hysterotomy to avoid the placenta, and expose pelvic sidewall and ureters
4. Be mindful of likely sources of massive bleeding: pelvic sidewall, bladder/vesicouterine space, and/or placenta previa vaginally
5. Proceed with meticulous dissection to minimize the risk of hemorrhage, retrograde fill the bladder, be mindful of the utility of packing
6. Be prepared to move to an expeditious hysterectomy in case of massive bleeding

When the PAS has extended laterally, perform stepwise division of the lateral attachments of the placenta to the pelvic sidewall using a combination of electrocautery, hemoclips, and the vessel-sealing device. In laterally extended PAS cases, it often is necessary to divide the uterine artery either at its origin or at the level of the ureter to allow for the completion of the separation of the placenta from the pelvic sidewall.

In our experience. During this lateral dissection, significant bleeding may be encountered from the neovascular network that has developed in the pelvic sidewall. The bleeding may be diffuse and difficult to control with the methods described above. In this situation, we have found that placing hemostatic agents in this area and packing the sidewall with laparotomy pads can achieve hemostasis in most cases, thus allowing the surgery to proceed.

Bladder dissection
The next critical part of the surgery involves developing the vesicovaginal space to mobilize the bladder. Prior to initiating the bladder dissection, we routinely retrograde fill the bladder with 180 to 240 mL of saline mixed with methylene blue. This delineates the areas with the highest risk of massive bleeding that can be difficult to control include the pelvic sidewall when there is lateral extension of the PAS, the vesicouterine space, and placenta previa vaginally.
superior edge of the bladder and indicates the appropriate level to start the dissection. Then slowly develop the vesicouterine space using a combination of electrocautery and a vessel-sealing device until the bladder is mobilized to the level of the anterior vaginal wall. Many vascular connections are encountered at that level, and meticulous dissection and patience is required to systematically divide them all.

In our experience. This part of the surgery presents several challenges. The bladder wall may be invaded by the placenta, which will lead to an increased risk of bleeding and cystotomy during the dissection. In these cases, it might be preferable to create an intentional cystotomy to guide the dissection; at times, a limited excision of the involved bladder wall may be required. In other cases, even in the absence of bladder wall invasion, the bladder may be densely adherent to the uterine wall (usually due to a history of prior CDts), and bladder mobilization may be complicated by bleeding from the neovascular network that has developed between the placenta and bladder.

**Uterine arteries and cervix**

Once the placenta is separated from its lateral attachments and the bladder is mobilized, the next steps are similar to those in a standard abdominal hysterectomy. If the uterine arteries were not yet divided during the pelvic sidewall dissection, they are clamped, divided, and suture ligated at the level of the uterine isthmus. The decision whether to perform a supracervical or total hysterectomy depends on the level of cervical involvement by the placenta, surgeon preference, anatomic distortion, and bleeding from the cervix and anterior vaginal wall.

**Responding to massive bleeding**

Not uncommonly, and despite the best efforts to avoid it, massive bleeding may develop from the areas at risk as noted above. If the bleeding is significant and originates from multiple areas (including vaginal bleeding from placenta previa), we recommend proceeding with an expeditious hysterectomy to remove the specimen, and then reassess the pelvic field for hemostatic control and any organ damage that may have occurred.

**The challenge of PAS**

Surgical management of PAS is one of the most challenging procedures in pelvic surgery. Successful outcomes require a multidisciplinary team approach and an experienced team dedicated to the management of this condition. By contrast, proceeding “as usual” in the face of an unexpected PAS situation can lead to disastrous consequences in terms of maternal morbidity and mortality.

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**References**

Requests for self-managed abortion via a telemedicine service increased by 27% from March 20, 2020, to April 11, 2020, in the United States in the wake of widespread lockdowns and shelter-in-place directives because of the COVID-19 pandemic, based on data from a provider of such services.

Access to abortion care is challenging in many areas under ordinary circumstances, but the disruption of the COVID-19 pandemic led to many states suspending or limiting in-clinic services, wrote Abigail R.A. Aiken, MD, PhD, of the University of Texas at Austin and colleagues. “As a result, people may increasingly be seeking self-managed abortion outside the formal health care system.”

In a research letter published in Obstetrics & Gynecology, the investigators reviewed request data from Aid Access, a telemedicine service that provides medication for abortion at up to 10 weeks’ gestation for users who complete an online consultation form. They also collected data on the implementation and scope of COVID-19–related interventions that could affect self-managed abortion.

Improving hand hygiene, optimizing antibiotic order sets, and removing catheters sooner were among the interventions associated with a decreased risk of infections after hysterectomy, according to research presented at the virtual annual scientific meeting of the Society of Gynecologic Surgeons.

“Implementation of bundled interventions and an institutional focus on reducing infection can successfully reduce the burden of posthysterectomy infectious morbidity,” said study author Shitanshu Uppal, MBBS, an ob.gyn. specializing in gynecologic oncology at the University of Michigan in Ann Arbor.

To assess the impact of quality improvement efforts on infectious morbidity after hysterectomy, Dr. Uppal and colleagues analyzed data from 1,867 hysterectomies performed between Oct. 8, 2015, and Oct. 7, 2018. Patients were at least 18 years old, younger than 90 years old, and underwent hysterectomy via any route at the University of Michigan Medical Center Hospital.

Interventions to reduce infections included the use of cefazolin as a preferred antibiotic, the addition of metronidazole to first-generation cephalosporins for antibiotic prophylaxis, subcuticular closure of open incisions, and earlier removal of Foley catheters. In addition, the institution evaluated and shared information about doctors’ practices.
The latest US Supreme Court decisions on contraception, transgender discrimination, more

Abortion, contraception, gay and transgender discrimination, and the ACA (again!). Here’s what every ObGyn should know about the most recent decisions of the Supreme Court.

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

The 2019–2020 term of the US Supreme Court was remarkable by any standard. An extraordinary number of important cases made it “a buffet of blockbusters.”

We look first at several cases that will be of particular interest to ObGyns. Then we look briefly at a number of other important cases that affect the medical profession as a whole and the direction of the country (see “Other significant US Supreme Court decisions”), and finally we conclude with an analysis of this term and a forecast for the next.

We chose cases in which specialty organizations, such as the American College of Obstetricians and Gynecologists (ACOG), or organized medicine (the American Medical Association [AMA], the Association of American Medical Colleges [AAMC], or the American Hospital Association [AHA]), took a special interest by filing “amicus curiae” (friend of the court) briefs with the Supreme Court. These briefs are filed by an organization or person who is not a party to the case but who may have important information to convey to the Court. Because these briefs represent a significant commitment of money, time, and effort, they are usually not undertaken lightly.

Decisions concerning abortion

June v Russo

Decided June 29, 2020, June v Russo involved a Louisiana statute that required abortion providers to have “active admitting privileges at a hospital” within 30 miles of where the abortion is performed. The Court decided a case in 2016 (from Texas) that involved almost the same statutory provision, so it might seem like an easy ruling. But Justice Kennedy (the deciding vote in 2016) has been replaced by Justice Gorsuch, so the outcome was uncertain. It was a difficult case, with a total of 5 opinions covering 138 pages and a “surprise” from the Chief Justice.

The Court, in a 5-4 decision, struck down the Louisiana law, but there was no
In June, SCOTUS struck down a state law requiring abortion providers to have admitting privileges at a hospital within 30 miles.

The American Association of Pro-Life Obstetricians and Gynecologists also filed an *amicus* brief. The brief was directed solely at arguing that ACOG was not presenting reliable science. It summarized, “The American College of Obstetricians and Gynecologists has always presented itself to the Court as a source of objective medical knowledge. However, when it comes to abortion, the College today is primarily a pro-abortion political advocacy organization.” That brief concluded that the “Court should read ACOG’s *amicus* brief not as an authoritative recitation of settled science, but as a partisan advocacy paper on behalf of a mere subset of American obstetricians and gynecologists.”

The American Association of Pro-Life Obstetricians and Gynecologists also filed an *amicus* brief. The brief argued, “Abortion, like other outpatient surgical procedures, sometimes results in patient hospitalization. Requiring abortion providers to maintain admitting privileges will improve communication between physicians in the transfer of patients to the hospital and allow them to participate in the care of their patients while in the hospital, in line with their ethical duty to ensure their patients’ continuity of care.”

CONTINUED ON PAGE 40
Ultrasonography requirement for abortion
In another abortion case, the Court was asked to review a Kentucky abortion statute requiring that an ultrasound image be shown to the woman as part of informed consent for an abortion. ACOG filed an amicus brief in favor of a review, but the Court declined to hear the case.10,11

Contraception considerations
The Affordable Care Act (ACA) has an ambiguous provision regarding no-cost “preventive care and screenings” for women. The ACA does not, however, specify contraceptive coverage.12 Several departments and the Health Resources and Services Administration (collectively referred to as “HRSA”) interpreted the provision to include contraception, but from the start there were religious objections. HRSA eventually provided an exemption regarding contraception for employers (nonprofits and for-profits with no publicly traded components) that had “sincerely held moral” objections to providing forms of contraceptive coverage. That regulation was again before the Court this term in Little Sisters of the Poor Saints Peter and Paul Home v Pennsylvania.13

In a 7-2 decision, the Court held that the ACA gave HRSA authority to adopt regulations related to the undefined term “preventive care.” Therefore, it found that HRSA could exempt those with religious objections from participation in providing contraceptive coverage. ACOG and other medical groups filed an amicus brief arguing that contraception is an essential preventive service. “Contraception not only helps to prevent unintended pregnancy, but also helps to protect the health and well-being of women and their children.”14 It was cited only by Justice Ginsburg in her dissent.15

Deferred Action for Childhood Arrivals (DACA)
The AAMC, ACOG, AMA, and many other organizations filed an amicus brief in Department of Homeland Security v Regents of University of California.17 The case raised the question of whether a decision to end the DACA program followed the appropriate administrative procedures. In 2012, the Obama administration issued a “memorandum” establishing DACA (without congresional approval or formal rulemaking). A lower court decision barring implementation of DACA was upheld by the Supreme Court in 2016 on a 4-4 vote.18 In 2017, the Trump administration moved to end DACA.

In a 5-4 decision, the Court held that the explanation for ending DACA was inadequate, and violated the Administrative Procedures Act, so DACA could continue until the administration redid the repeal, following the proper procedures. The decision of the Court dealt solely with the process by which the rescission took place—there was general agreement that the administration had the right to rescind it if the procedure (with legitimate reasons) was proper.

The brief for the medical groups argued that the failure of the regulation to consider “reliance interests” would have especially difficult consequences in the medical fields. It noted, “At this moment, an estimated 27,000 health care workers and support staff depend on DACA for their authorization to work in the United States. Among those 27,000 are nurses, dentists, pharmacists, physician assistants, home health aides, technicians, and others. The number also includes nearly 200 medical students, medical residents, and physicians who depend on DACA for their eligibility to practice medicine.”16 The brief was not cited by the Court, but the reliance interest the brief spoke about was an important part of the case.

Employment discrimination against gay and transgender employees
Federal law (“Title VII”) makes it illegal for an employer to “discriminate against any individual because of race, color, religion, sex, or national origin.”19 The question this term was whether discrimination based on sexual
Other significant US Supreme Court decisions

The Court heard and ruled on a large number of other significant cases that will have consequences for many years to come. Highlights include:

• In 2 cases involving subpoenas for the President’s personal records, the Court suggested some balance between “nobody is above the law” and not unnecessarily hectoring or interfering with fulfilling the office of President. The Court held that Congress may subpoena a President’s personal and family records, while the President is still in office. It instructed lower courts to assess whether the papers are necessary, the subpoena is limited in scope, there is legitimate legislative purpose, whether the burden it imposes on the President is reasonable, and whether the subpoena would unduly interfere with the ability to do the work required as President.

• Similarly, local (state) grand juries may subpoena such personal records, but the President will have the opportunity to raise specific objections to the subpoenas—undue burden, bad faith, or overbreadth. In addition, the respect owed to the office should inform the conduct regarding the subpoena.

• The Court upheld a federal law that prohibits most robocalls. It struck down an amendment that allowed robocalls made to collect debts owed to or guaranteed by the federal government.

• The Court held that a single-director federal agency, whose director cannot be removed by the President (at will), violates the Constitution. The Consumer Financial Protection Bureau (created by the Dodd-Frank law) has such a single, no-removal director and that will have to be modified.

• The Court held that the eastern half of Oklahoma (including Tulsa) is part of a Creek Nation reservation. This was a question of criminal law jurisdiction, not property ownership. The practical effect is that for crimes involving Native Americans, serious crimes will have to be tried in federal court, while lesser crimes may be tried in tribal courts.

• The Court determined that it was unconstitutional for a state program providing tuition assistance to parents who send their children to private schools, to prohibit students attending religious private schools from participating in the program. That is a burden on the “free exercise” of religion.

• The Court considered whether there can be civil liability for damages caused by a federal official in the United States harming a foreign national in another country. In this case, a border patrol agent standing in the US shot and killed a Mexican juvenile who was just across the border in Mexico. The issue was whether the parents of the Mexican national could sue the US officials for damages. The Court declined to expand liability to include those injured outside the US. Ultimately, the Court was reluctant to impose liability because this liability is not authorized by Congress.

• In a COVID-19 religion case, the Court refused to stop the enforcement of a governor’s COVID-19 order that allowed churches to operate with <100 attendees or 25% occupancy (whichever was lower). Meanwhile, businesses, malls, and stores were allowed to reopen without these stringent limitations. The church objected that greater burdens were placed on religion than secular activity. The Court denied the church’s request for an injunction.

• The Court unanimously held that a state may punish or remove a “faithless elector.” Electors cast votes on behalf of their states in the Electoral College—where Presidents are technically selected. Electors are generally pledged to vote for the winner of a state’s vote for President. A few have violated that pledge and voted for someone else. As a practical matter, that could cause real disruption, and the Court upheld state laws that take action against these “faithless” electors.

• Several days after the Court had officially adjourned for the term, it received several petitions to delay the execution of federal prisoners. One case was based on the method of execution (use of pentobarbital), and another was based on the claim that a prisoner had become so mentally incompetent that it was improper to execute him. The Court turned down these appeals, allowing the executions to proceed. These were the first federal government executions in 17 years.

References
orientation or sexual identity is within the statute’s meaning of “sex.” By a 6-3 majority, the Court held that Title VII applies both to orientation and identity. (This was an interpretation of the statute, not a broad constitutional ruling.)

The majority reasoned that “it is impossible to discriminate against a person for being homosexual or transgender without discriminating against that individual based on sex. Consider, for example, an employer with 2 employees, both of whom are attracted to men.” If the employer fires the gay employee, “the employer discriminates against him for traits or actions it tolerates in his female colleague.”20

AMA and a number of other medical organizations filed an amicus brief in the case.21 The core of the argument of the brief was, “Employment discrimination against transgender people frustrates the treatment of gender dysphoria by preventing transgender individuals from living openly in accordance with their true gender identity and impeding access to needed medical care. Experiencing discrimination in one of the most important aspects of adult life—employment—makes it nearly impossible to live in full congruence with one’s gender identity. The fear of facing such discrimination alone can prompt transgender individuals to hide their gender identity, directly thwarting the goal of social transition…. Lack of treatment, in turn, increases the rate of negative mental health outcomes, substance abuse, and suicide.” The brief was not cited in the opinions in the case.

This decision is likely to have great impact on many aspects of American life. In the employment area, it is now a matter of course that employers may not discriminate based on orientation or identity in any employment decisions including hiring, firing, compensation, fringe benefits, etc. Harassment based on identity or orientation may similarly be an employment law violation. The decision also likely means that giving employment preferences to gay employees would now be as illegal as would be giving preferences to straight employees. (Limited exceptions, notably to some religious organization employees, are not included in antidiscrimination laws.)22

The importance of the decision goes well beyond employment, however. More than 100 federal statutes are in place that prohibit “discrimination because of sex.” It is now likely that these statutes will be interpreted as prohibiting discrimination related to sexual orientation and identification.

Additional cases of interest
HIV/AIDS International Program
A major US program fighting HIV/AIDS worldwide—the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act (aka the Leadership Act)—has provided billions of dollars to agencies abroad.23 Non-governmental organizations (NGOs) receiving funds under the program must agree to have a “policy explicitly opposing prostitution and sex trafficking” (known as the “Policy Requirement”). Some grant recipients in foreign countries, generally affiliates of US NGOs, do not want to have such a policy and challenged the policy requirement as a violation of First Amendment right of free speech. The Court held that it is a well-settled principle that “foreign citizens outside US territory do not possess rights under the US Constitution.”24 Nor do organizations become entitled to such rights as a result of an affiliation with US organizations. This decision means that foreign organizations are free not to have the required policies, but they will be ineligible for funds under the Leadership Act.

ACA government debts edition
The ACA was before the Court, yet again. To encourage private insurers to participate in online health insurance exchanges, the ACA provided that the federal government would share in insurance company losses for 3 years.25 The Act, however, did not appropriate any money for these “risk corridors,” and insurance companies lost $12 billion.

Congress (after the 2010 election) prohibited any appropriated funds from being used to pay insurance companies for their risk corridor losses. Four insurance companies...
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RBG: The woman, the legacy

Ruth Bader Ginsburg, as a law student, law professor, lawyer, judge, and justice, was a leading advocate for the rights of women. There were only a few women in law school when she attended, but she graduated tied for first in her class. Although she found it difficult to be hired as a lawyer, as a law professor and lawyer she helped map a strategy to expand legal rights for women, arguing 6 cases before the Supreme Court and winning 5 of them. She served as a federal appeals court judge and then was appointed to the Supreme Court in 1993. She was the second woman to serve on the Court.

As a justice, she was known during much of her tenure on the Court as the leader of the liberal justices, although her jurisprudence was more complex than that simple statement. She was always a strong advocate for the rights of women (and equal rights of men) during her time on the Court. She was a very clear writer; her opinions were direct and easy to understand. She was also fast—she routinely had the record of announcing opinions faster than any of the other current justices. She was 87 when she passed away, having served on the Court for 27 years.

Justice Ginsburg was also something of a cultural phenomenon. In later years she was sometimes known as “the Notorious RBG.” Books, movies, songs, and even workout videos were made about her. In groups she seemed almost shy, but she was thoughtful, kind, and funny (sometimes wickedly so). The outpouring of affection and sympathy at her death was a symbol of the place she held in America. She loved the opera, a passion she shared with her friend, Justice Antonin Scalia. Despite their considerable disagreements on legal matters, Justices Ginsburg and Scalia were close friends. They attended opera with one another, and their families usually spent New Year’s Eves together. They were the 2 most recent justices to pass away while serving on the Court.

The courts of the country where the child has “habitual residence” have jurisdiction to decide custody.27 If a parent takes the child to another country, that country is obligated to return the child to the country of “habitual residence.”

This term the Court was called upon to define “habitual residence.” The Court held that determining habitual residence depends on the “totality of the circumstances,” and that “locating a child’s home is a fact-driven inquiry,” and that “courts must be sensitive to the unique circumstances of the case and informed by common sense.”28 An exception to the Convention’s obligation to return a child to the country of habitual residence is where “there is a grave risk that [the] return would expose the child to physical or psychological harm or otherwise place the child in an intolerable situation.”29 Who the parent is can affect many aspects of legal authority over the child, including consent to medical care, and the right to receive information concerning care.

Analysis of the term

The term began October 7, 2019, and adjourned July 9, 2020, somewhat later than usual because of coronavirus disease 2019 (COVID-19). During the term, the Court decided 60 cases, including 53 “signed” merit opinions after oral argument—the lowest number of decided cases in many years.30 Of those 60 cases, 22 (35%) were unanimous, and 13 (22%) resulted in a 5-4 split.30 Ten-year averages are 48% unanimous and 20% with 5-4 decisions.30

Chief Justice Roberts was the central focus of the term. He presided over the impeachment trial of President Trump in the Senate early in the term. He also presided over the Court’s accommodations of the COVID-19 pandemic. He is the “median,” or “swing,” justice. He was in the majority in 12 of the 13 cases with 5-4 decisions.30 He was in the majority in 97% of all cases and in 95% of “divided cases”—the highest of any of the justices this term.30 In some of the most critical decisions, Chief
Justice Roberts sided with the “liberal” wing, including on cases concerning abortion, gay and transgender employment, DACA, and 2 Presidential subpoena cases. More often (in 9 of the 5-4 decisions), however, he sided with the more conservative justices. Justice Kavanaugh agreed with Chief Justice Roberts most often (in 93% of all cases). Among the others, these justices agreed with each other 90% or more of the time: Justices Ginsburg and Breyer (93%), Justices Alito and Thomas (92%), and Justices Breyer and Kagan (90%).

COVID-19 and the Court

Some of the biggest news of the term came not from the law, but from medicine in the form of COVID-19. The Court was in the process of preparing a final period of important arguments when, on March 16, it announced that it was postponing further arguments. The Court rescheduled 10 oral arguments that were held by telephone (other cases were held over to the next term). The phone arguments, during the first 2 weeks of May, necessitated a change in format. Each justice was called on (in order of seniority) by the Chief Justice to ask questions. This was in contrast to the free-for-all questions that usually characterize in-person arguments. These arguments were broadcast live—something that had never been done before. Public access was, on balance, a good thing. There were a couple failures to unmute, and there was “the flush heard round the world” in the middle of one argument, but otherwise the arguments went off with few hitches.

Looking ahead

By the end of the term, no justice had announced an intention to retire from the Court. At least 2 justices were hospitalized during the term—Justice Ginsburg was hospitalized twice for gallbladder-related issues. Following the end of the term, she announced a recurrence of pancreatic cancer; she is receiving chemotherapy (gemcitabine). Chief Justice Roberts was briefly hospitalized for a minor injury.

The next term (called the “October 2020 Term”) will begin on October 5, 2020. Most are assuming that it will be telephonic. The Court already has taken a number of cases. The constitutionality of the individual mandate (coverage) in the ACA will once again be before the Court, and that already has produced a flood of amicus briefs from health-related organizations.

Among other upcoming issues are cases related to the sentencing of juveniles to life in prison without the possibility of parole, state regulation of pharmacy benefit managers, a face-off between Google and Oracle on software copyrights, and arbitration. In addition, the next term will include a return of some of the issues we saw this term, with more on robocalls, religious freedom and Catholic charities, and immigration and removal cases.

References


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What's the VERDICT?

CONTINUED FROM PAGE 45


11. EMW Women’s Surgical Center, PSC v Meier, 140 S. Ct. 655 (2019).

12. Codified at 26 U.S.C. §5000A(f)(2); §§4980H(a), (c)(2) requires employers to provide women with “preventive care and screenings” without “any cost sharing requirements.”


Expanding Contraceptive Choices for Women: The Vaginal pH Modulator

Vaginal pH modulators (VPMs) add a new class of contraception that is now available in the United States. This method is nonhormonal, woman-controlled, and coitally dependent—and has the potential to increase overall contraceptive use and potentially reduce unintended pregnancy rates.

This CME supplement to OBG Management focuses on VPMs, their attributes, and the methodology surrounding the determination of contraceptive effectiveness.
Apps for applying to ObGyn residency programs in the era of virtual interviews

The pandemic has required program and student flexibility and innovation. These authors offer help for navigating the process.

Farida Nentin, MD, and Katherine T. Chen, MD, MPH

The coronavirus disease 2019 (COVID-19) pandemic has upended the traditional 2020–2021 application season for ObGyn residency programs. In May 2020, the 2 national ObGyn education organizations, the Association of Professors of Gynecology and Obstetrics (APGO) and Council on Resident Education in ObGyn (CREOG), issued guidelines to ensure a fair and equitable application process. These guidelines are consistent with recommendations from the Association of American Medical Colleges (AAMC) and the Coalition for Physician Accountability. Important recommendations include:

- limiting away rotations
- being flexible in the number of specialty-specific letters of recommendation required
- encouraging residency programs to develop alternate means of conveying information about their curriculum.

In addition, these statements provide timing on when programs should release interview offers and when to begin interviews. Finally, programs are required to commit to online interviews and virtual visits for all applicants, including local students, rather than in-person interviews.

Here, we focus on identifying apps that students can use to help them with the application process—apps for the nuts and bolts of applying and interviewing and apps to learn more about individual programs.

Students must use the Electronic Residency Application Service (ERAS) platform from AAMC to enter their information and register with the National Resident Matching Program (NRMP). Students also must use the ERAS to submit their applications to their selected residency programs. The ERAS platform does not include an app to aid in the completion or submission of an application. The NRMP has developed the MATCH PRISM app, but this does not allow students to register for the match or submit their rank list. To learn about how to schedule interviews, residency programs may use...
one of the following sources: ERAS, Interview Broker, or Thalamus. Moreover, APGO/CREOG has partnered with Thalamus for the upcoming application cycle, which provides residency programs and applicants tools for application management, interview scheduling, and itinerary building. Thalamus offers a free app.

This year offers some unique challenges. The application process for ObGyn residencies is likely to be more competitive, and students face the added stress of having to navigate the interview season:

- without away rotations (audition interviews)
- without in-person visits of the city/hospital/program or social events before or after interview day
- with an all-virtual interview day.

To find information on individual residency programs, the APGO website lists the FREIDA and APGO Residency Directories, which are not apps. Students are also aware of the Doximity Residency Navigator, which does include an app. The NRMP MATCH PRISM app is another resource, as it provides students with a directory of residency programs and information about each program.

The American College of Obstetricians and Gynecologists (ACOG) recognizes that residency program websites and social media will be crucial in helping applicants learn about individual programs, faculty, and residents. As such, ACOG hosted a Virtual Residency Showcase in September 2020 in which programs posted content on Instagram and Twitter using the hashtag #ACOG-ResWeek20. Similarly, APGO and CREOG produced a report containing a social media directory, which lists individual residency programs and whether or not they have a social media handle/account. In a recent webinar, Drs. Sarah Santiago and Elizabeth Southworth noted that the number of residency programs that have an Instagram account more than doubled (from 60 to 128) between May and September 2020.

We present 2 tables describing the important features and caveats of apps available to students to assist them with residency applications this year—TABLE 1 summarizes apps to aid with applications and interviews; TABLE 2 lists apps designed for students to learn more about individual residency programs. We wish all of this year’s students every success in their search for the right program.

### TABLE 1 Recommended apps to aid with ObGyn residency applications and interviews

<table>
<thead>
<tr>
<th>App</th>
<th>Platform</th>
<th>Important features</th>
<th>Caveats</th>
</tr>
</thead>
</table>
| The MATCH PRISM app, by the National Resident Matching Program (NRMP) | • Free app available for iOS and Android | • Has residency match schedule of events  
• Creates personal lists of programs  
• Syncs with Outlook which allows for tracking application and interview schedule  
• Allows user free-text notes about program | • Cannot schedule interviews with programs  
• Cannot submit NRMP rank list |
| Thalamus | • Free app available for iOS and Android | • Allows online scheduling of interviews in real time  
• Streamlines communication between program and applicant  
• Manages confirmations, rescheduling, waitlists, and cancellations | • Cannot use software to conduct virtual interviews |

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<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Apps designed for students to learn more about individual residency programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRMP MATCH PRISM app</td>
<td>Provides students with a directory of residency programs and information about each program.</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Offers online scheduling of interviews in real time, streamlines communication between program and applicant, manages confirmations, rescheduling, waitlists, and cancellations.</td>
</tr>
</tbody>
</table>

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*ACOG Residency Directories: https://www.acog.org/Residency-Directories  
*FREIDA: https://freida.acog.org  
*NRMP MATCH PRISM app: https://www.nrmp.org/match-prism  
*Thalamus: https://www.thalamus.com  
*In a recent webinar, Drs. Sarah Santiago and Elizabeth Southworth noted that the number of residency programs that have an Instagram account more than doubled (from 60 to 128) between May and September 2020.  
*The Tables are adapted from the American College of Obstetricians and Gynecologists (ACOG) and the Accreditation Council for Graduate Medical Education (ACGME).
### TABLE 2  Recommended apps to learn about ObGyn residency programs

<table>
<thead>
<tr>
<th>App</th>
<th>Platform</th>
<th>Important features</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residency Navigator on the Doximity app</td>
<td>Free app available for iOS and Android</td>
<td>Includes: • Ratings and reviews from current residents and alumni • Program information about top feeder schools and alumni destinations • Easy search function for programs by specialty and location • Filtering of programs by hospital type, intended fellowship, training environment • Creation of a list of favorite programs • User can add free-text notes about program</td>
<td>• Information about programs is collected by residents and alumni from surveys • Large systems with multiple residency programs can have inaccurate information about top feeder schools, resident and alumni information, and board passage rates</td>
</tr>
<tr>
<td>The MATCH PRISM app, by the National Resident Matching Program (NRMP)</td>
<td>Free app available for iOS and Android</td>
<td>Includes tabs with: • Residency match schedule of events • Directory of all residency programs participating in The Match with direct links to programs • 20-factor rating system to aid in program selection • Easy search function to locate programs by specialty and location • User free-text notes about program</td>
<td>• Cannot schedule interviews with programs • Cannot submit NRMP rank list</td>
</tr>
<tr>
<td>Instagram</td>
<td>Free app available for iOS and Android</td>
<td>• Accounts are managed by the residency programs and updated frequently • Offers an inside look to happenings within each program—social, advocacy, wellness, research, etc</td>
<td>• Out of 241 ObGyn residency programs, only 155 programs have Instagram accounts* • Users must search for programs by keywords or hashtags</td>
</tr>
<tr>
<td>Twitter</td>
<td>Free app available for iOS and Android</td>
<td>• Accounts are managed by the residency program • App offers an inside look to happenings within the program—social, advocacy, wellness, research, etc • Programs post updates frequently</td>
<td>• Out of 241 ObGyn residency programs, only 66 programs have Twitter accounts* • Users must search for programs by keywords or hashtags</td>
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### References

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