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OBG MANAGEMENT

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*Statistical significance for dyspareunia was not achieved with the 150 mg QD dose of ORILISSA.

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.

OVER 10,000 HCPs HAVE ALREADY PRESCRIBED ORILISSA FOR MORE THAN 30,000 patients[2,3†]

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[4-6]

> "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

Consider ORILISSA for your patients like Darby with unresolved endometriosis pain[4,6]

†These data reflect the number of HCPs who have prescribed and the number of women prescribed since ORILISSA was FDA-approved. Data were sourced as of September and October 2019, respectively.

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.

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

References: 1. AbbVie receives U.S. FDA approval of Orilissa™ (elagolix) for the management of moderate to severe pain associated with endometriosis [press release]. North Chicago, IL: AbbVie Inc; July 24, 2018. https://news.abbvie.com/news/abbvie-receives-us-fda-approval-orilissa-elagolix-for-management-moderate-to-severe-pain-associated-with-endometriosis.htm. Accessed August 28, 2019. **2.** Data on file. AbbVie Inc. ORILISSA cumulative writers. IQVIA data from DSL; August 2018 - September 2019.**3.** Data on file. AbbVie Inc. ORILISSA NBRx. IQVIA and UBC/Medvantx; August 2018 - October 2019. **4.** Orilissa [package insert]. North Chicago, IL: AbbVie Inc. **5.** Data on file. ABVRRTI65829. **6.** Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28-40.

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

Orilissa®
elagolix tablets 150 mg 200 mg

ORILISSA® (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ORILISSA is indicated for the management of moderate to severe pain associated with endometriosis.

DOSAGE AND ADMINISTRATION

Important Dosing Information

- Exclude pregnancy before starting ORILISSA or start ORILISSA within 7 days from the 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

Dosing Regimen	Maximum Treatment Duration	Coexisting Condition
Initiate treatment with ORILISSA 150 mg once daily	24 months	None
Consider initiating treatment with ORILISSA 200 mg twice daily	6 months	Dyspareunia
Initiate treatment with ORILISSA 150 mg once daily. Use of 200 mg twice daily is not recommended.	6 months	Moderate hepatic impairment (Child-Pugh Class B)

Hepatic Impairment

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

Compared to women with normal liver function, those with moderate hepatic impairment had approximately 3-fold higher elagolix exposures and those with severe hepatic impairment had approximately 7-fold higher elagolix exposures. Because of these increased exposures and risk for bone loss:

- ORILISSA 150 mg once daily is recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months. Use of ORILISSA 200 mg twice daily is not recommended for women with moderate hepatic impairment *[see Use in Specific Populations]*.
- ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications and Use in Specific Populations]*.

Missed Dose

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

- 150 mg once daily: take no more than 1 tablet each day.
- 200 mg twice daily: take no more than 2 tablets each day.

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

- Who are pregnant *[see Use in Specific Populations]*. Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss.
- 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 concomitant use of strong organic anion transporting 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 after stopping treatment *[see Adverse Reactions]*. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. Consider assessment of BMD in patients with a history of a 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.

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 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 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

Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials. ORILISSA subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history *[see Adverse Reactions]*. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits *[see Adverse Reactions]*. 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.

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 of ORILISSA 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 *[see Adverse Reactions]*.

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 with ORILISSA and for one week after discontinuing ORILISSA *[see Use in Specific Populations, Drug Interactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Bone loss *[see Warnings and Precautions]*
- Change in menstrual bleeding pattern and reduced ability to recognize pregnancy *[see Warnings and Precautions]*
- Suicidal ideation, suicidal behavior, and exacerbation of mood disorders *[see Warnings and Precautions]*
- Hepatic transaminase elevations *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety of ORILISSA was evaluated in two six-month, randomized, double-blind, placebo-controlled clinical trials [EM-1 (NCT01620528) and EM-2 (NCT01931670)] in which a total of 952 adult women with moderate to severe pain associated with endometriosis were treated with ORILISSA (475 with 150 mg once daily and 477 with 200 mg twice daily) and 734 were treated with placebo. The population age range was 18-49 years old. Women who completed six months of treatment and met eligibility criteria continued treatment in two uncontrolled, blinded six-month extension trials [EM-3 (NCT01760954) and EM-4 (NCT02143713)], for a total treatment duration of up to 12 months.

Serious Adverse Events

Overall, the most common serious adverse events reported for subjects treated with ORILISSA in the two placebo-controlled clinical trials (Studies EM-1 and EM-2) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%). In these trials, 0.2% of subjects treated with ORILISSA 150 mg once daily and 0.2% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to serious adverse reactions compared to 0.5% of those given placebo.

Adverse Reactions Leading to Study Discontinuation

In the two placebo-controlled clinical trials (Studies EM-1 and EM-2), 5.5% of subjects treated with ORILISSA 150 mg once daily and 9.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to adverse reactions compared to 6.0% of those given placebo. Discontinuations were most commonly due to hot flushes or night sweats (1.1% with 150 mg once daily and 2.5% with 200 mg twice daily) and nausea (0.8% with 150 mg once daily and 1.5% with 200 mg twice daily) and were dose-related. The majority of discontinuations due to hot flushes or night sweats (10 of 17, 59%) and nausea (7 of 11, 64%) occurred within the first 2 months of therapy.

In the two extension trials (Studies EM-3 and EM-4), discontinuations were most commonly due to decreased BMD and were dose-related. In these trials, 0.3% of subjects treated with ORILISSA 150 mg once daily and 3.6% of subjects treated with ORILISSA 200 mg twice daily discontinued therapy due to decreased BMD.

Common Adverse Reactions:

Adverse reactions reported in ≥ 5% of women in the two placebo-controlled trials in either ORILISSA dose group and at a greater frequency than placebo are noted in the following table.

Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Emergent Adverse Reactions Occurring in at Least 5% of Subjects (either ORILISSA Dose Group) and at a Greater Incidence than with Placebo

	ORILISSA 150 mg Once Daily N=475	ORILISSA 200 mg Twice Daily N=477	Placebo N=734
	%	%	%
Hot Flush or Night Sweats	24	46	9
Headache	17	20	12
Nausea	11	16	13
Insomnia	6	9	3
Mood altered, mood swings	6	5	3
Amenorrhea	4	7	<1
Depressed mood, depression, depressive symptoms and/or tearfulness	3	6	2
Anxiety	3	5	3
Arthralgia	3	5	3

Less Common Adverse Reactions:

In Study EM-1 and Study EM-2, adverse reactions reported in ≥ 3% and < 5% in either ORILISSA dose group and greater than placebo included: decreased libido, diarrhea, abdominal pain, weight gain, dizziness, constipation and irritability.

The most commonly reported adverse reactions in the extension trials (EM-3 and EM-4) were similar to those in the placebo-controlled trials.

Bone Loss

The effect of ORILISSA on BMD was assessed by dual-energy X-ray absorptiometry (DXA).

In Studies EM-1 and EM-2, there was a dose-dependent decrease in BMD in ORILISSA-treated subjects compared to an increase in placebo-treated subjects.

In Study EM-1, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -0.9% (95% CI: -1.3, -0.4) with ORILISSA 150 mg once daily and -3.1% (95% CI: -3.6, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was 2% with ORILISSA 150 mg once daily, 7% with ORILISSA 200 mg twice daily and < 1% with placebo. In the blinded extension Study EM-3, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 8% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

In Study EM-2, compared to placebo, the mean change from baseline in lumbar spine BMD at 6 months was -1.3% (95% CI: -1.8, -0.8) with ORILISSA 150 mg once daily and -3.0% (95% CI: -3.5, -2.6) with ORILISSA 200 mg twice daily (Table 3). The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the placebo-controlled treatment period was < 1% with ORILISSA 150 mg once daily, 6% with ORILISSA 200 mg twice daily and 0% with placebo. In the blinded extension Study EM-4, continued bone loss was observed with 12 months of continuous treatment with ORILISSA. The percentage of subjects with greater than 8% BMD decrease in lumbar spine, total hip or femoral neck at any time point during the extension treatment period was 2% with continuous ORILISSA 150 mg once daily and 21% with continuous ORILISSA 200 mg twice daily.

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

	ORILISSA 150 mg Once Daily	ORILISSA 200 mg Twice Daily	Placebo
EM-1			
N	183	180	277
Percent Change from Baseline, %	-0.3	-2.6	0.5
Treatment Difference, % (95% CI)	-0.9 (-1.3, -0.4)	-3.1 (-3.6, -2.6)	
EM-2			
N	174	183	271
Percent Change from Baseline, %	-0.7	-2.5	0.6
Treatment Difference, % (95% CI)	-1.3 (-1.8, -0.8)	-3.0 (-3.5, -2.6)	

To assess for recovery, the change in lumbar spine BMD over time was analyzed for subjects who received continuous treatment with ORILISSA 150 mg once daily or ORILISSA 200 mg twice daily for up to 12 months and who were then followed after cessation of therapy for an additional 6 months. Partial recovery of BMD was seen in these subjects (Figure 1).

In Study EM-3, if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip at the end of treatment, follow-up DXA was required after 6 months off-treatment. In Study EM-4, all subjects were required to have a follow-up DXA 6 months off treatment regardless of change in BMD and if a subject had BMD loss of more than 1.5% at the lumbar spine or more than 2.5% at the total hip after 6 months off treatment, follow-up DXA was required after 12 months off-treatment. Figure 2 shows the change in lumbar spine BMD for the subjects in Study EM-2/EM-4 who completed 12 months of treatment with ORILISSA and who had a follow-up DXA 12-months off treatment.

Figure 1. 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-2/EM-4

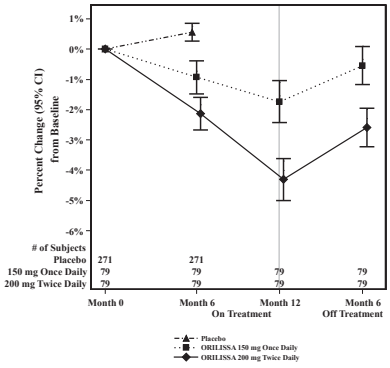
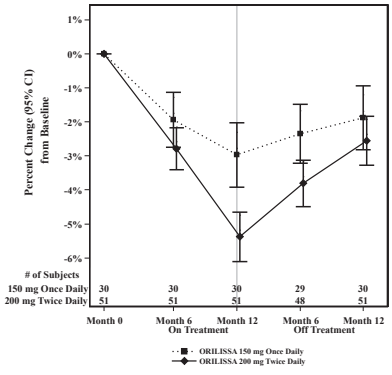


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

In the placebo-controlled trials (Studies EM-1 and EM-2), ORILISSA was associated with adverse mood changes (see Table 2 and Table 4), particularly in those with a history of depression.

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

	ORILISSA		
Adverse Reactions	**150 mg Once Daily (N=475) n (%)**	**200 mg Twice Daily (N=477) n (%)**	**Placebo (N=734) n (%)**
Completed suicide	1 (0.2)	0	0
Suicidal ideation	1 (0.2)	1 (0.2)	0

A 44-year-old woman received 31 days of ORILISSA 150 mg once daily then completed suicide 2 days after ORILISSA discontinuation. She had no relevant past medical history; life stressors were noted.

Among the 2090 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-3 (150 mg once daily) and one in a Phase 2 study (75 mg once daily, an unapproved dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment periods.

Hepatic Transaminase Elevations

In the placebo-controlled clinical trials (Studies EM-1 and EM-2), dose-dependent asymptomatic elevations of serum ALT to at least 3-times the upper limit of the reference range occurred during treatment with ORILISSA (150 mg once daily – 1/450, 0.2%; 200 mg twice daily – 5/443, 1.1%; placebo – 1/696, 0.1%). Similar increases were seen in the extension trials (Studies EM-3 and EM-4).

Changes in Lipid Parameters

Dose-dependent increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and serum triglycerides were noted during ORILISSA treatment in EM-1 and EM-2. In EM-1 and EM-2, 12% and 1% of subjects with mildly elevated LDL-C (130-159 mg/dL) at baseline had an increase in LDL-C concentrations to 190 mg/dL or higher during treatment with ORILISSA and placebo, respectively. In EM-1 and EM-2, 4% and 1% of subjects with mildly elevated serum triglycerides (150-300 mg/dL) at baseline had an increase in serum triglycerides to at least 500 mg/dL during treatment with ORILISSA and placebo, respectively. The highest measured serum triglyceride concentration during treatment with ORILISSA was 982 mg/dL.

Table 5. Mean Change and Maximum Increase from Baseline in Serum Lipids in Studies EM-1 and EM-2

	ORILISSA 150 mg Once Daily N=475	**ORILISSA 200 mg Twice Daily N=477**	**Placebo N=734**
LDL-C (mg/dL)			
Mean change at Month 6	5	13	-3
Maximum increase during Treatment Period	137	107	122
HDL-C (mg/dL)			
Mean change at Month 6	2	4	1
Maximum increase during Treatment Period	43	52	45
Triglycerides (mg/dL)			
Mean change at Month 6	<1	11	-3
Maximum increase during Treatment Period	624	484	440

Lipid increases occurred within 1 to 2 months after the start of ORILISSA and remained stable thereafter over 12 months.

Hypersensitivity Reactions

In Studies EM-1 and EM-2, non-serious hypersensitivity reactions including rash occurred in 5.8% of ORILISSA treated-subjects and 6.1% of placebo-treated subjects. These events led to study drug discontinuation in 0.4% of ORILISSA-treated subjects and 0.5% of placebo-treated subjects.

Endometrial Effects

Endometrial biopsies were performed in subjects in Study EM-1 and its extension at Month 6 and Month 12. These biopsies showed a dose-dependent decrease in proliferative and secretory biopsy patterns and an increase in quiescent/minimally stimulated biopsy patterns. There were no abnormal biopsy findings on treatment, such as endometrial hyperplasia or cancer.

Based on transvaginal ultrasound, during the course of a 3-menstrual cycle study in healthy women, ORILISSA 150 mg once daily and 200 mg twice daily resulted in a dose-dependent decrease from baseline in mean endometrial thickness.

Effects on menstrual bleeding patterns

The effects of ORILISSA on menstrual bleeding were evaluated for up to 12 months using an electronic daily diary where subjects classified their flow of menstrual bleeding (if present in the last 24 hours) as spotting, light, medium, or heavy. ORILISSA led to a dose-dependent reduction in mean number of bleeding and spotting days and bleeding intensity in those subjects who reported menstrual bleeding.

Table 6. Mean Bleeding/Spotting Days and Mean Intensity Scores at Month 3

	ORILISSA 150mg Once Daily		**ORILISSA 200mg Twice Daily**		**Placebo**	
	Base-line	**Month 3**	**Base-line**	**Month 3**	**Base-line**	**Month 3**
Mean bleeding/ spotting days in prior 28 days	5.3	2.8	5.7	0.8	5.4	4.6
Mean Intensity score[a]	2.6	2.2	2.5	2.0	2.6	2.4

[a]Intensity for subjects who reported at least 1 day of bleeding or spotting during 28 day interval. Scale ranges from 1 to 4, 1 = spotting, 2 = light, 3 = medium, 4 = heavy

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 during the first six months of treatment ranged from 6-17% for ORILISSA 150 mg once daily, 13-52% for ORILISSA 200 mg twice daily and less than 1% for placebo. During the second 6 months of treatment, the incidence of amenorrhea ranged from 11-15% 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 59%, 87% and 95% 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 resumption of menses after stopping treatment was reported by 77%, 95% and 98% of women within 1, 2, and 6 months respectively. After 12 months of therapy with ORILISSA 200 mg twice daily resumption of menses after stopping treatment was reported by 55%, 91% 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 inducer of cytochrome P450 (CYP) 3A. Co-administration with ORILISSA may decrease plasma concentrations of drugs that are substrates of CYP3A.

Elagolix is a weak inhibitor of CYP 2C19. Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of CYP2C19 (e.g., omeprazole).

Elagolix is an inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ORILISSA may increase plasma concentrations of drugs that are substrates of P-gp (e.g., digoxin).

Potential for Other Drugs to Affect ORILISSA

Elagolix is a substrate of CYP3A, P-gp, and OATP1B1.

Concomitant use of ORILISSA 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and strong CYP3A inhibitors to 6 months.

Co-administration of ORILISSA with drugs that induce CYP3A may decrease elagolix plasma concentrations.

The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ORILISSA is unknown. Co-administration of ORILISSA with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations. Concomitant use of ORILISSA and strong OATP1B1 inhibitors (e.g., cyclosporine and gemfibrozil) is contraindicated.

Drug Interactions - Examples and Clinical Management

Table 7 summarizes the effect of co-administration of ORILISSA on concentrations of concomitant drugs and the effect of concomitant drugs on ORILISSA.

Table 7. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	**Effect on Plasma Exposure of Elagolix or Concomitant Drug**	**Clinical Recommendations**
Antiarrhythmics digoxin	↑ digoxin	Clinical monitoring is recommended for digoxin when co-administered with ORILISSA.
Antimycobacterial rifampin	↑ elagolix	Concomitant use of ORILISSA 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months.
Benzodiazepines oral midazolam	↓ midazolam	Consider increasing the dose of midazolam and individualize therapy based on the patient's response.
Statins rosuvastatin	↓ rosuvastatin	Consider increasing the dose of rosuvastatin.
Proton pump inhibitors omeprazole	↑ omeprazole	No dose adjustments are needed for omeprazole at doses of 40 mg once daily or lower. When ORILISSA is used concomitantly with higher doses of omeprazole, e.g. in patients with Zollinger-Ellison syndrome, consider dosage reduction of omeprazole.

The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑= increase, ↓ = decrease).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors outcomes in women who become pregnant while treated with ORILISSA. Patients should be encouraged to enroll by calling 1-833-782-7241.

Risk Summary

Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss. Use of ORILISSA is contraindicated in pregnant women. Discontinue ORILISSA if pregnancy occurs during treatment.

The limited human data with the use of ORILISSA in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage. Although two cases of congenital malformations were reported in clinical trials with ORILISSA, no pattern was identified and miscarriages were reported at a similar incidence across treatment groups *(see Data)*.

When pregnant rats and rabbits were orally dosed with elagolix during the period of organogenesis, postimplantation loss was observed in pregnant rats at doses 20 times the maximum recommended human dose (MRHD). Spontaneous abortion and total litter loss was observed in rabbits at doses 7 and 12 times the MRHD. There were no structural abnormalities in the fetuses at exposures up to 40 and 12 times the MRHD for the rat and rabbit, respectively *(see Data)*.

The background risk for major birth defects and miscarriage in the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

There were 49 pregnancies reported in clinical trials of more than 3,500 women (of whom more than 2,000 had endometriosis) treated with ORILISSA for up to 12 months. These pregnancies occurred while the women were receiving ORILISSA or within 30 days after stopping ORILISSA. Among these 49 pregnancies, two major congenital malformations were reported. In one case of infant cleft palate, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 30 days of pregnancy. In one case of infant tracheoesophageal fistula, the mother was treated with ORILISSA 150 mg daily and the estimated fetal exposure to ORILISSA occurred during the first 15 days of pregnancy.

Among these 49 pregnancies, there were five cases of spontaneous abortion (miscarriage) compared to five cases among the 20 pregnancies that occurred in more than 1100 women treated with placebo. Although the duration of fetal exposure was limited in ORILISSA clinical trials, there were no apparent decreases in birth weights associated with ORILISSA in comparison to placebo.

Animal Data

Embryofetal development studies were conducted in the rat and rabbit. Elagolix was administered by oral gavage to pregnant rats (25 animals/dose) at doses of 0, 300, 600 and 1200 mg/kg/day and to rabbits (20 animals/dose) at doses of 0, 100, 150, and 200 mg/kg/day, during the period of organogenesis (gestation day 6-17 in the rat and gestation day 7-20 in the rabbit).

In rats, maternal toxicity was present at all doses and included six deaths and decreases in body weight gain and food consumption. Increased postimplantation losses were present in the mid dose group, which was 20 times the MRHD based on AUC. In rabbits, three spontaneous abortions and a single total litter loss were observed at the highest, maternally toxic dose, which was 12 times the MRHD based on AUC. A single total litter loss occurred at a lower non-maternally toxic dose of 150 mg/kg/day, which was 7 times the MRHD.

No fetal malformations were present at any dose level tested in either species even in the presence of maternal toxicity. At the highest doses tested, the exposure margins were 40 and 12 times the MRHD for the rat and rabbit, respectively. However, because elagolix binds poorly to the rat gonadotropin-releasing hormone (GnRH) receptor (~1000 fold less than to the human GnRH receptor), the rat study is unlikely to identify pharmacologically mediated effects of elagolix on embryofetal development. The rat study is still expected to provide information on potential non-target-related effects of elagolix.

In a pre- and postnatal development study in rats, elagolix was given in the diet to achieve doses of 0, 100 and 300 mg/kg/day (25 per dose group) from gestation day 6 to lactation day 20. There was no evidence of maternal toxicity. At the highest dose, two dams had total litter loss, and one failed to deliver. Pup survival was decreased from birth to postnatal day 4. Pups had lower birth weights and lower body weight gains were observed throughout the pre-weaning period at 300 mg/kg/day. Smaller body size and effect on startle response were associated with lower pup weights at 300 mg/kg/day. Post-weaning growth, development and behavioral endpoints were unaffected.

Maternal plasma concentrations in rats on lactation day 21 at 100 and 300 mg/kg/day (47 and 125 ng/mL) were 0.06-fold and 0.16-fold the maximal elagolix concentration (C_{max}) in humans at the MRHD. Because the exposures achieved in rats were much lower than the human MRHD, this study is not predictive of potentially higher lactational exposure in humans.

Lactation

Risk Summary

There is no information on the presence of elagolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. There are no adequate animal data on the excretion of ORILISSA in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORILISSA and any potential adverse effects on the breastfed child from ORILISSA.

Data

There are no adequate animal data on excretion of ORILISSA in milk.

Females and Males of Reproductive Potential

Based on the mechanism of action, there is a risk of early pregnancy loss if ORILISSA is administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

Exclude pregnancy before initiating treatment with ORILISSA. Perform pregnancy testing if pregnancy is suspected during treatment with ORILISSA *[see Warnings and Precautions]*.

Contraception

Advise women to use effective non-hormonal contraception during treatment with ORILISSA and for one week after discontinuing ORILISSA *[see Warnings and Precautions and Drug Interactions]*.

Pediatric Use

Safety and effectiveness of ORILISSA in patients less than 18 years of age have not been established.

Renal Impairment

No dose adjustment of ORILISSA is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis).

Hepatic Impairment

No dosage adjustment of ORILISSA is required for women with mild hepatic impairment (Child-Pugh A). Only the 150 mg once daily regimen is recommended for women with moderate hepatic impairment (Child-Pugh B) and the duration of treatment should be limited to 6 months.

ORILISSA is contraindicated in women with severe hepatic impairment (Child-Pugh C) *[see Contraindications]*.

OVERDOSAGE

In case of overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate symptomatic treatment, as needed.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid

(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

Advise 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 1-833-782-7241 *[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]*.
- Counsel 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 soon 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.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

Manufactured by AbbVie Inc.
North Chicago, IL 60064

Ref: 03-C007 Revised: August, 2019

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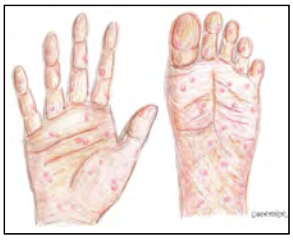

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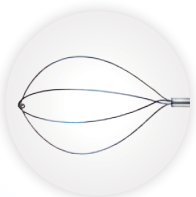

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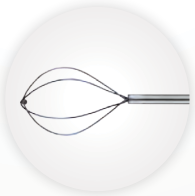

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ABBY SCHULTZ, MD

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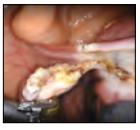

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9vHPV vaccine: Prevention of oropharyngeal cancer

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.

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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.[1] In the same year, the investigators reported 11,788 cases of cervical cancer.[1] 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.[1]

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.[2] 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.[3]

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.[4-7]

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%).[7] 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.[8] 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

doi: 10.12788/obgm.0050

A woman searching for birth control online

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.

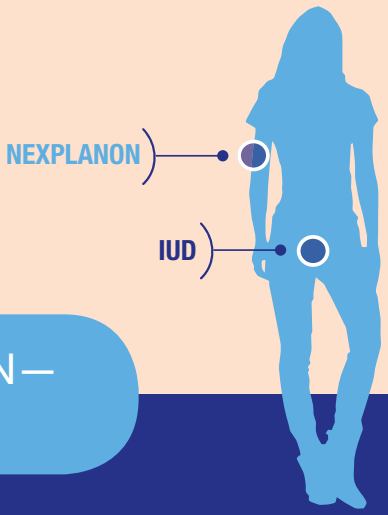
NEXPLANON and pregnancy

- 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.

MERCK
INVENTING FOR LIFE

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Nexplanon®
(etonogestrel implant) 68mg

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

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

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

Complications of Insertion and Removal

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

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

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

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

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

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

Changes in Menstrual Bleeding Patterns

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

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

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

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

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

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

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

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

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

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

Ectopic Pregnancies

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

Thrombotic and Other Vascular Events

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

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

Ovarian Cysts

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

Carcinoma of the Breast and Reproductive Organs

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

Liver Disease

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

Weight Gain

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

Elevated Blood Pressure

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Depressed Mood

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

Return to Ovulation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Effects of Other Drugs on Hormonal Contraceptives
Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.

Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*

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

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

For more detailed information, please read the Prescribing Information.
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CONTINUED FROM PAGE 9

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.[1] It is also approved for males aged 9 to 45 years to prevent cancer and precancers of the anus 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."[2]

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls and boys, 11 to 12 years of age.[1] 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[3] (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.

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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; $P = .008$).[9] Among men, oral HPV 16/18/6/11 was lower among those vaccinated versus unvaccinated (0.0% and 2.13%, respectively; $P = .007$).[9] 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.[10] By contrast, among men, the rates of self-reported vaccination were much lower—8% in 2013 and 27% in 2018.[10]

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.[10] For men, these percentages were 2% in 2013 and 9% in 2018.[10] 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.[11] 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.[1] 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.[2]

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.[3] 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.[4] 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%).[4] 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.[4] 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.[5] HPV DNA was detected in 95% of the cervical samples, 30% of the surgical smoke samples, and 1.5% of the surgeons' nasal swabs.[5] 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[6] and laryngeal papillomatosis[7] 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.[6] The gynecologist had performed more than 3,000 laser ablation or LEEP procedures of dysplastic cervical, vaginal, and vulvar lesions over a span of 20 years.[6] Most of the procedures were performed without wearing a mask and in a poorly ventilated procedure room. A computed tomography scan demonstrated a 2.2-cm soft tissue lesion in the right tonsil extending to the right soft palate and a level-2 lymph node. A biopsy of the tonsil confirmed invasive squamous cell carcinoma containing HPV16. He was treated with 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.[8,9] **In February 2020, the American Society for Colposcopy and Cervical Pathology recommended that clinicians who are routinely exposed to HPVs consider 9vHPV vaccination.**[8] 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.

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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."[11]

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. ●

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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.

Carvalho Gazarra LB, Bonacordi CL, Yela DA, et al. Bone mass in women with premature ovarian insufficiency: a comparative study between hormone therapy and combined oral contraceptives. Menopause. 2020;27:1110-1116.

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.

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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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

FAST TRACK

Although 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

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,[5] 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.

in women who used no treatment or low-dose EPT.[1]

Other studies' take on dose, route of administration, and cost considerations

Sequelae of POI include infertility, bothersome hot flashes, vaginal dryness, sexual dysfunction, mood disorders, and an elevated risk of cardiovascular disease, dementia, Parkinson's disease, and osteoporosis. Importantly, clinicians and patients need to understand that the results from the Women's Health Initiative studies do *not* apply to women with POI.[2] Physiologic doses of HT (that is, doses higher than those used to treat menopausal symptoms in women with normal/spontaneous menopause) are appropriate for women with POI, at least until they reach the normal age of menopause (51 to 52 years).

A clinical trial conducted in Scotland in women with POI found that high-dose transdermal estrogen (application of one to two 0.1-mg estradiol patches) daily had an impact on BMD that was more positive than that of an oral contraceptive formulated with EE 30 µg.[3] Likewise, a trial in the United States found that, among oligo-amenorrheic athletes, a hormone replacement regimen using a 0.1-mg estradiol patch had a more positive impact on BMD than an oral contraceptive formulated with EE 30 µg.[4]

Although Carvalho Gazarra and colleagues acknowledged awareness of reports suggesting the skeletal health benefits of high-dose estradiol patches, in the Brazilian public health system oral hormone therapy is less expensive and oral contraceptives are available at no charge.[1] ●

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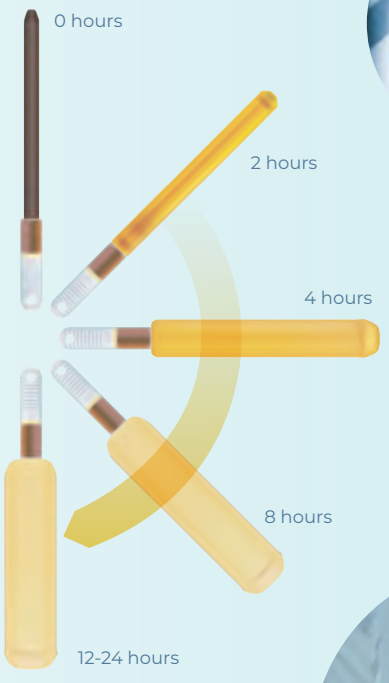

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medicem

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

IN THIS ARTICLE

CASE Pregnant woman with positive *Treponema pallidum* antibody test

A 30-year-old primigravida 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?

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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.[1,2] *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.[3] *T pallidum* can cross the placenta and infect a fetus as early as the sixth week of gestation.[3] 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.[4,5] Additionally, syphilis infection is associated with a high risk of HIV infection, as well as coinfection with other STIs.[1]

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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FIGURE 1 The chancre that is characteristic of primary syphilis

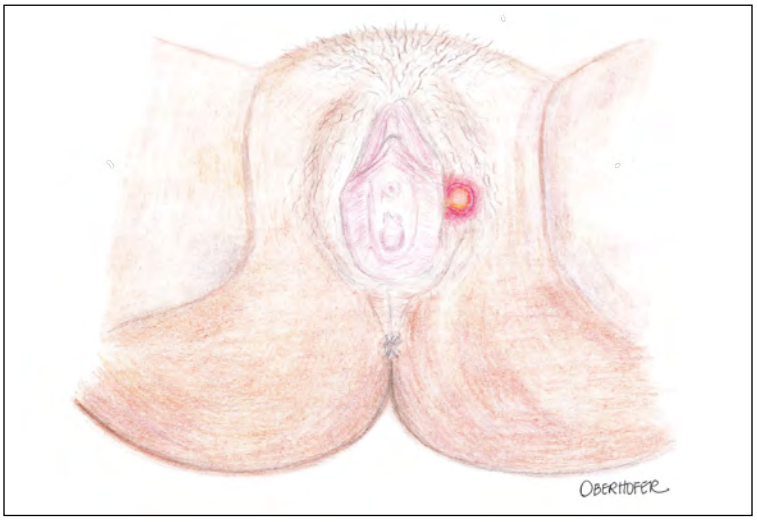

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FIGURE 2 The characteristic rash of secondary syphilis

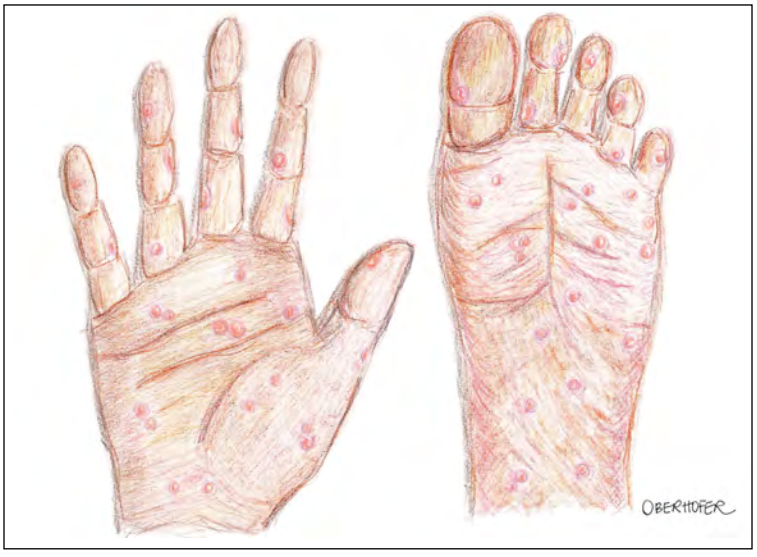

Image courtesy of Haley Oberhofer.

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.[6] 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.[6] 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.[6]

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).[3] 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.[6] 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.[5,7]

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**). Chancres most commonly appear in the genital area, with the most frequent sites in females being within the vaginal canal or on the cervix. Primary chancres 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.[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 *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 (**FIGURE 2**); mucosal lesions, such as mucous patches and condyloma lata (**FIGURE 3**); nonscarring alopecia; periostitis; generalized lymphadenopathy; and, in some cases, hepatitis or nephritis.[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.[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.[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.[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 (**FIGURE 4**) and cardiovascular manifestations including arterial aneurysms and aortic insufficiency.[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).[1,5] Patients with late (tertiary)

FIGURE 3 Condyloma lata, which is characteristic of secondary syphilis

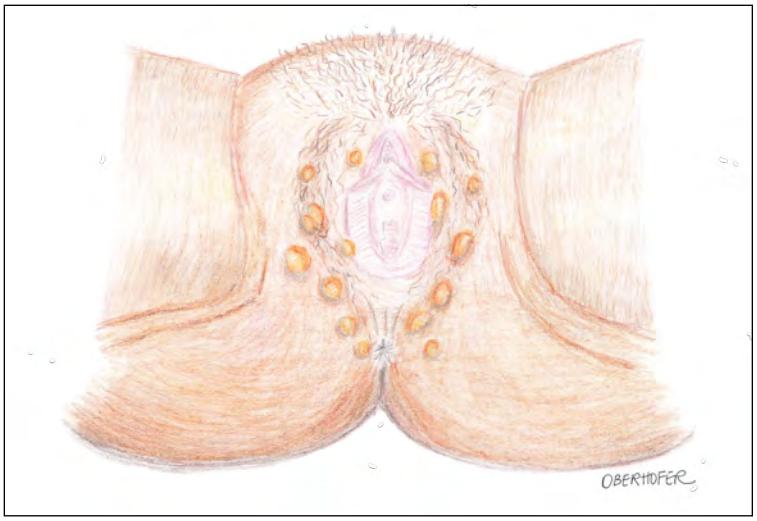

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FIGURE 4 The gumma, the characteristic mucocutaneous lesion of tertiary syphilis

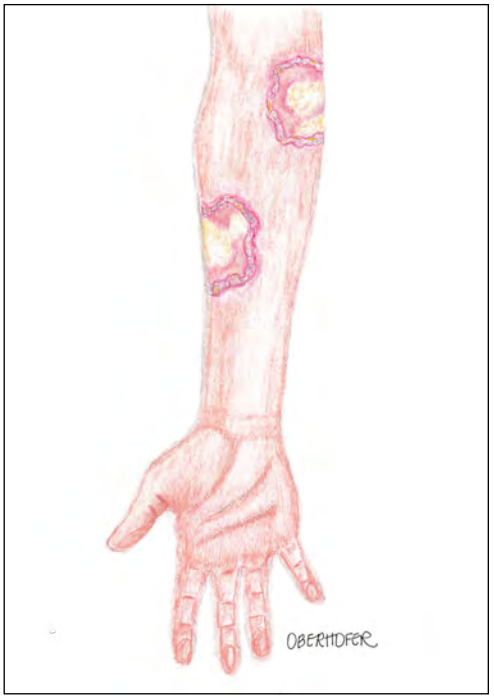

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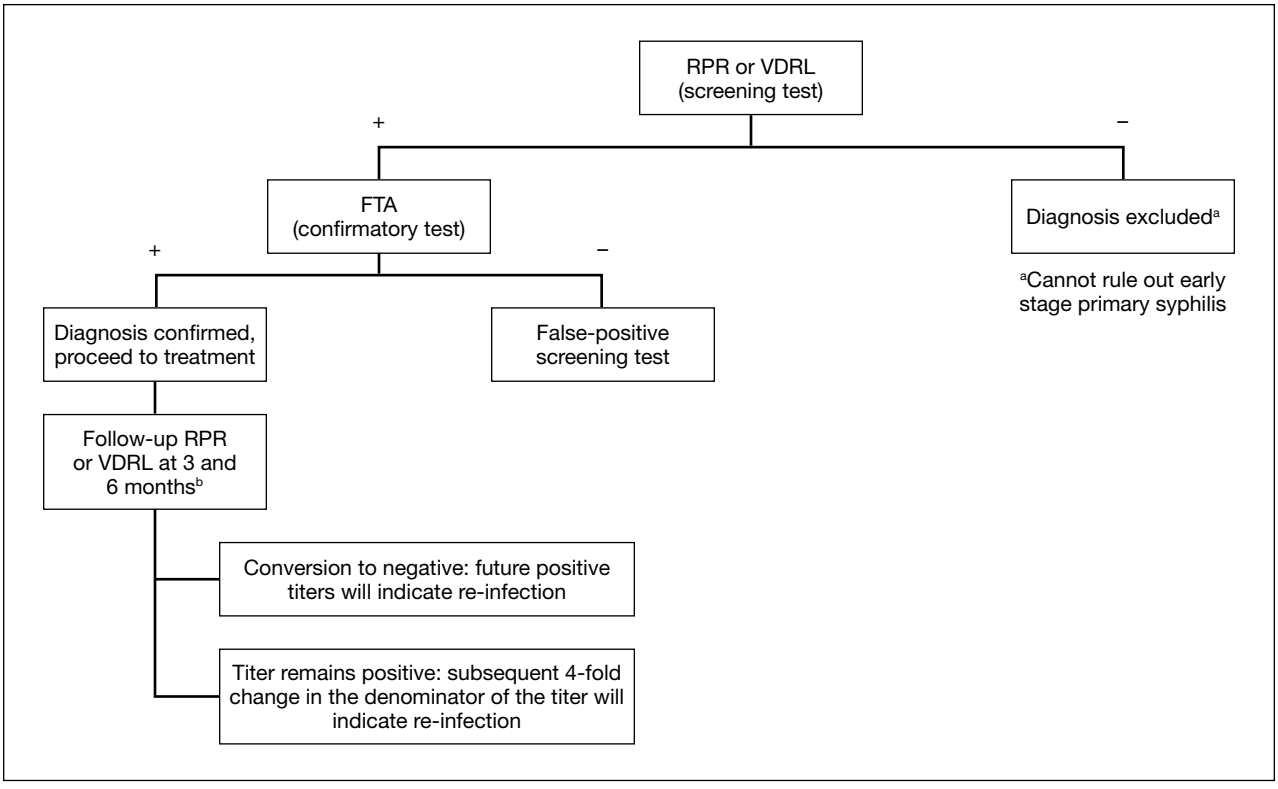
FIGURE 5 Traditional syphilis screening algorithm



[b]Follow-up titers should be ordered at 3 and 6 months to determine efficacy of treatment and to establish a baseline titer for future screening. A subsequent 4-fold increase in the denominator of this titer (ie, 1:8 → 1:32) indicates re-infection and a need for repeat treatment.

Abbreviations: FTA, fluorescent treponemal antibody; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

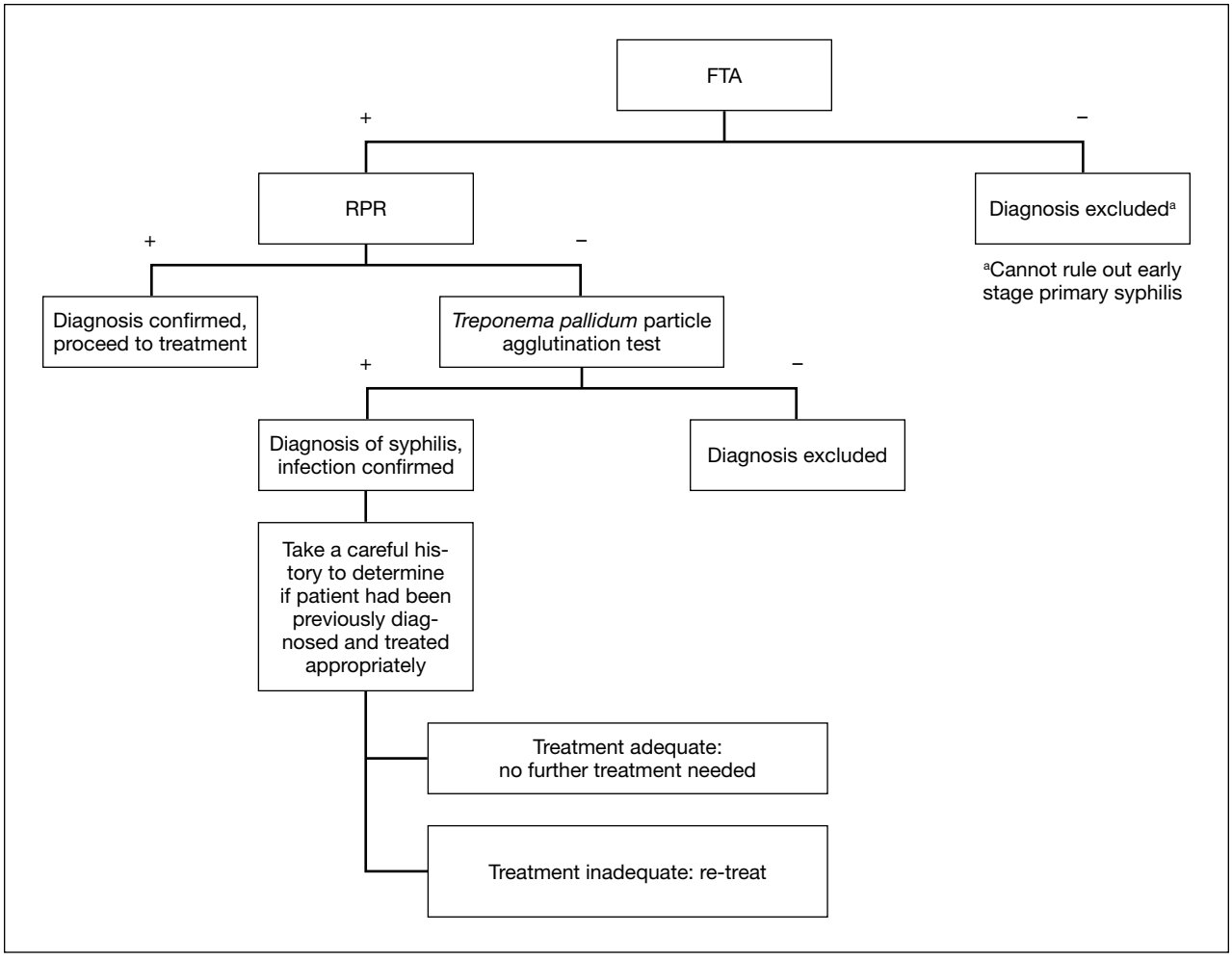
neurosyphilis tend to exhibit meningovascular symptoms similar to stroke (aphasia, hemiplegia, seizures) and/or parenchymal effects such as general paresis. Tabes dorsalis (manifestations of which include urinary and rectal incontinence, lightning pains, and ataxia) is a late-onset manifestation.[1,3]

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

FIGURE 6 Reverse screening algorithm for syphilis



Abbreviations: FTA, fluorescent treponemal antibody; RPR, rapid plasma reagin.

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

TABLE Common presentations and treatment of syphilis in pregnancy

Stage of disease	Characteristic manifestation	Treatment regimen
Primary	Chancre	Benzathine penicillin G, 2.4 million units IM in a single dose[a]
Secondary	• Diffuse maculopapular rash that includes the palms and soles • Condyloma lata • Mucous patches • Alopecia	Benzathine penicillin G, 2.4 million units IM in a single dose[a]
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[a]
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 • CVA • General paresis • Dementia	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 OR Procaine penicillin, 2.4 million units IM/day, plus probenecid 500 mg orally every day, both for 10-14 days

[a]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.

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.[11] 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.[11] While reverse screening has been found to incur higher costs, and may result in overtreatment and increased stress due to false-positive results,[12] there is evidence to suggest that this algorithm is more sensitive for primary and latent infections.[8,11,13-15]

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

treating established fetal infections.[3,5] 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.[5] Any patient with diagnosed syphilis who demonstrates clinical signs of neurologic involvement should undergo lumbar puncture to assess for evidence of neurosyphilis.[3] 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.[3,5]

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.[5] 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.[16] 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, placentomegaly, or hydrops.[5,7]

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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BREAK THIS PRACTICE HABIT

Maternal oxygen in labor: False reassurance?

These experts offer evidence for why ObGyns should stop the liberal use of maternal oxygenation to manage abnormal FHR tracings

Sally Harris, MD, and Georgia Ragonetti-Zebell, MD

IN THIS ARTICLE

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.[1] Maternal oxygen is used to treat abnormal FHR tracings in approximately half of all births in the United States.[2] 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.[3]

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.[4] Their data showed that maternal oxygen

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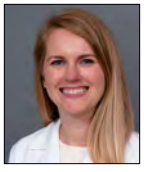

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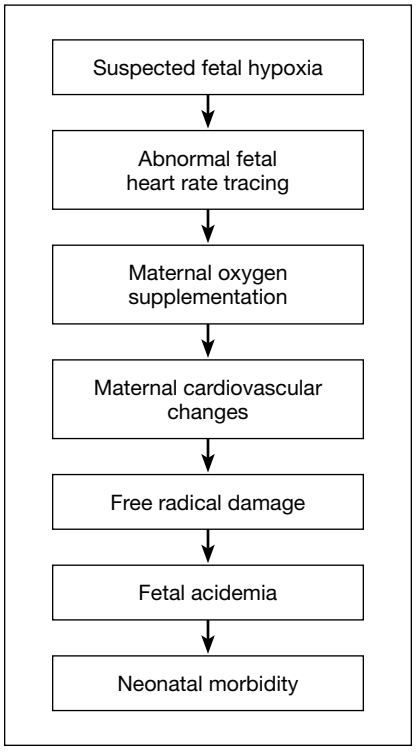
administration increased fetal oxygen as measured by fetal pulse oximetry. The lower the initial fetal oxygen levels prior to oxygen administration, the greater the increase.

Despite these findings, evidence for improved neonatal outcomes is lacking.[5] 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 hyperoxygenation 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.

FIGURE Effects of maternal oxygen supplementation during labor on the neonate



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.[6] 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 hyperoxygenation 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.[7] 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.[8] 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 acidemic, 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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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

IN THIS ARTICLE

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.[1] Notably, in women with PAS, the rate of hysterectomy is 52.2%, and the transfusion-dependent hemorrhage rate is 46.9%.[1]

Ideally, PAS should be diagnosed or at least suspected antenatally during prenatal ultrasonography, leading to delivery planning by a multidisciplinary team.[2] 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.[3-5]

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.

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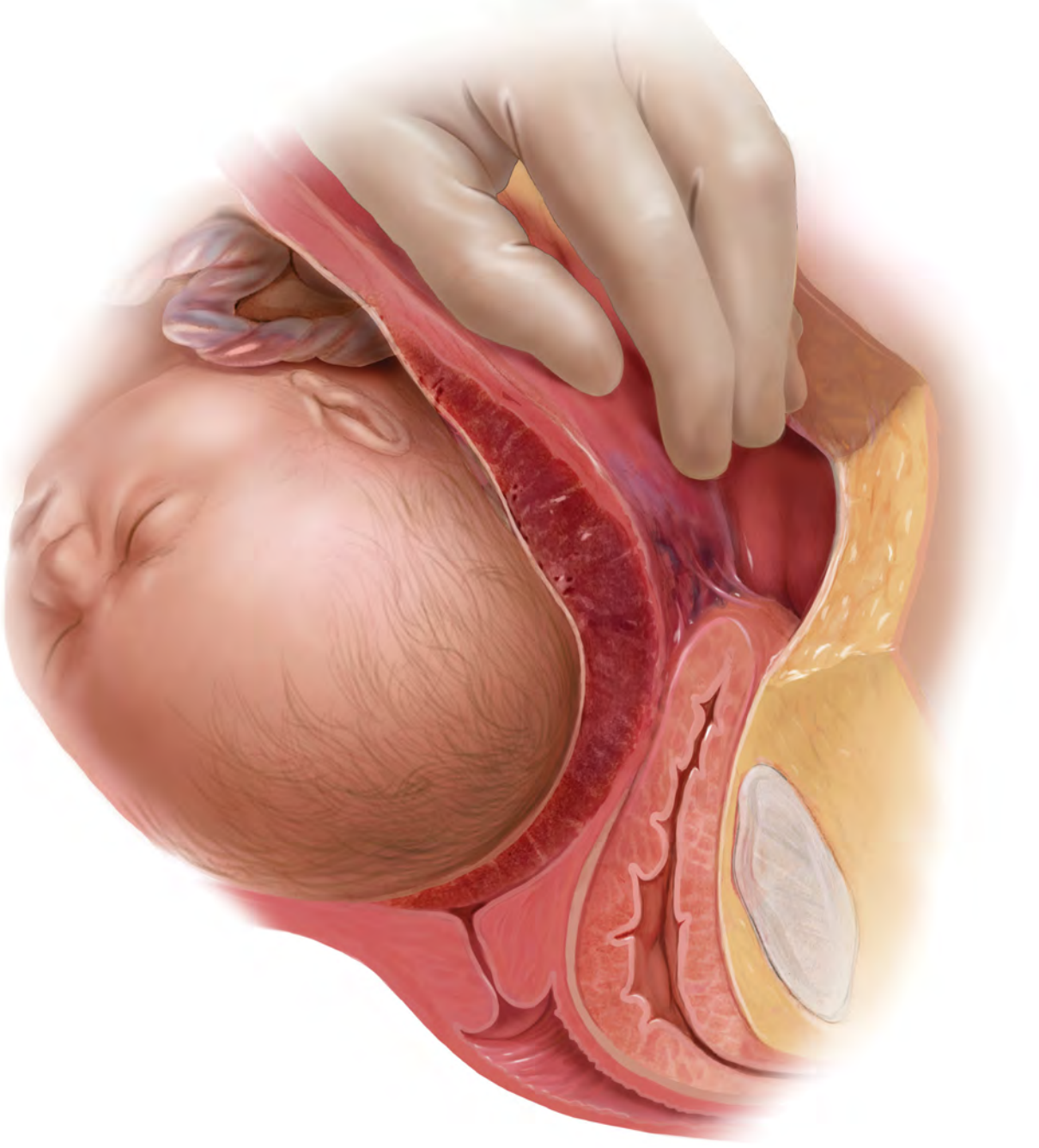


ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Stop and collect your multidisciplinary team

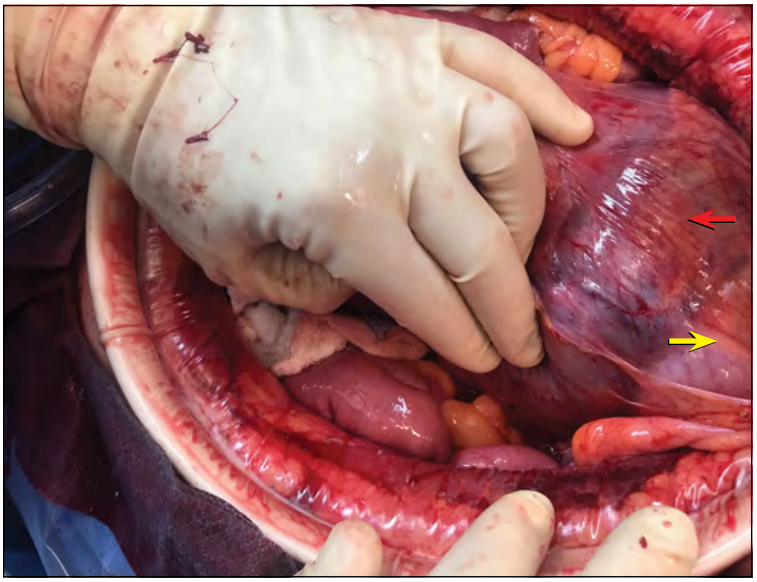
Once the diagnosis of an advanced PAS is suspected, the first step is to stop and request the presence of your institution's multidisciplinary surgical team. This team typically includes a maternal-fetal specialist or, if not available, an experienced obstetrician, and an expert pelvic surgeon, which 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

FIGURE Lower uterine segment suspicious for placenta accreta spectrum



Red arrow: placenta/lower uterine segment. Yellow arrow: bladder.

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

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.[6]

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.[7]

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

FAST TRACK

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 CDs), 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 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.[9] 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. ●

FAST TRACK

If bleeding is significant and originates from multiple areas, we recommend proceeding with an expeditious hysterectomy and then reassessing the pelvic field for hemostatic control and any organ damage

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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

IN THIS ARTICLE

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."[1]

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.

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Decisions concerning abortion

June v Russo

Decided June 29, 2020, *June v Russo* involved a Louisiana statute that required abortion providers have "active admitting privileges at a hospital" within 30 miles of where the abortion is performed.[2] The Court decided a case in 2016 (from Texas) that involved almost the same statutory provision, so it might seem like an easy ruling.[3] 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

majority opinion. Four justices in the plurality emphasized that the Louisiana law (like the Texas law) substantially burdened the right to abortion without any corresponding benefit to the health of the women seeking abortions. (Under earlier Court precedents, "undue burdens" on abortion are unconstitutional.[4]) Justice Breyer noted that the state could not present even one example in which a woman would have had better treatment if her doctor had admitting privileges. For a variety of reasons, admitting privileges were cumbersome for abortion providers to obtain; therefore, enforcing the law had little or no benefit, but significant risk of reduced availability of abortion services.

In *June v Russo,* Chief Justice Roberts literally became the "swing vote"—the fifth vote to strike down the Louisiana law. In 2016, he had voted the other way—to uphold essentially the same law (in Texas) that he struck down here. He attributed his switch to precedent (the general obligation of courts to follow prior decisions). He disagreed with the earlier decision, but felt bound by it.

This should be the end of the abortion provider "hospital privileges requirements" that a number of states have passed. States seeking to nibble away at abortion rights will undoubtedly look elsewhere. Beyond that, it is difficult, from this case, to discern the future of abortion rights.

ACOG was the lead in *amicus* briefs urging the Court to strike down the Louisiana law. ACOG (with others) was one of only a handful of organizations filing a brief urging the Court to agree to hear the case.[5] When the Court did agree to hear the case ("granted *certiorari"*), ACOG and a number of other medical organizations filed a formal *amicus* brief on the merits of the case.[6] The brief made 2 arguments: First, that this case was essentially decided in *Whole Woman's Health* in 2016 (the Texas case) and, second, that "an admitting privileges requirement is not medically necessary" and "clinicians who provide abortions are unable to obtain admitting privileges for reasons unrelated to their ability to safely and competently perform abortions." Justice Breyer cited the ACOG brief twice.

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The American Association of Pro-Life Obstetricians and Gynecologists also filed an *amicus* brief.[7] 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 Association of American Physicians and Surgeons (which should not be confused with the "National Board of Physicians and Surgeons") 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."[8]

FAST TRACK

In June, SCOTUS struck down a state law requiring abortion providers to have admitting privileges at a hospital within 30 miles

CONTINUED ON PAGE 40

CONTINUED FROM PAGE 39

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.[9] 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]

FAST TRACK

SCOTUS upheld the religious exemption for contraception coverage in the ACA

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[16] 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 congressional 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.[1] 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.[2]
- The Court upheld a federal law that prohibits most robocalls.[3] 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.[4] 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.[5] 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.[6]
- 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.[7] 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).[8] 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.[9]
- 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),[10] and another was based on the claim that a prisoner had become so mentally incompetent that it was improper to execute him.[11] The Court turned down these appeals, allowing the executions to proceed. These were the first federal government executions in 17 years.

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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.

FAST TRACK

SCOTUS interpreted "sex" in Title VII (which makes it illegal for employers to discriminate against race, color, religion, sex, or national origin) as including sexual orientation and sexual identity

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] Nongovernmental 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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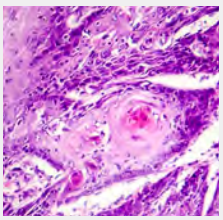

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RBG: The woman, the legacy

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.

sued the United States, seeking reimbursements for their losses. This term the Court held that the government must pay for their losses under the ACA.[26] The Court said that Congress could have expressly repealed the risk corridor obligation (in the appropriation bill), but instead had only prohibited the expenditure of the money, which the Court said did not amount to an implied repeal of the obligation. We will see that ACA will be back before the Court again next term in California v Texas (discussed below).

Child custody and international abduction

The Hague Convention on the Civil Aspects of International Child Abduction (to which the United States is a party) provides that 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.[30] Justice Kavanaugh agreed with Chief Justice Roberts most often (in 93% of all cases).[30] 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%).[30]

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.[31]

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.[32]

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. ●

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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.[1] 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

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

App	Platform	Important features	Caveats
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

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 #ACOGResWeek20.[2] 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.[3] In a recent webinar,[4] 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 2 Recommended apps to learn about ObGyn residency programs

App	Platform	Important features	Caveats
Residency Navigator on the Doximity app	• Free app available for iOS and Android	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	• 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
The MATCH PRISM app, by the National Resident Matching Program (NRMP)	• Free app available for iOS and Android	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	• Cannot schedule interviews with programs • Cannot submit NRMP rank list
Instagram	• Free app available for iOS and Android	• Accounts are managed by the residency programs and updated frequently • Offers an inside look to happenings within each program—social, advocacy, wellness, research, etc	• Out of 241 ObGyn residency programs, only 155 programs have Instagram accounts[a] • Users must search for programs by keywords or hashtags
Twitter	• Free app available for iOS and Android	• 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	• Out of 241 ObGyn residency programs, only 66 programs have Twitter accounts[a] • Users must search for programs by keywords or hashtags

[a]Sarah Santiago and Elizabeth Southworth unpublished data. APGO webinar: Virtual interviews best practices. September 9, 2020. https://zoom.us/rec/play/KqxMT6Wn-bF6qaMnFMoer_czOszRGRT89o364GHDzhFpjXodgSyGZpj0BaCvKnXtxD7IH-u1IU4QIzHBT.etDUC4znlfNcgG7T?startTime=1599696020000.

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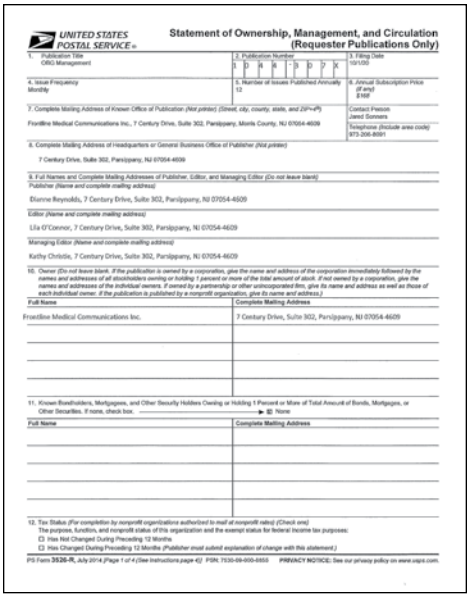

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Editor (Name and complete mailing address): Lia O'Connor, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609
Managing Editor (Name and complete mailing address): Kathy Christie, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609
10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)

Full Name	Complete Mailing Address
Frontline Medical Communications Inc.	7 Century Drive, Suite 302, Parsippany, NJ 07054-4609

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box. → ☒ None

Full Name	Complete Mailing Address

12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement.)

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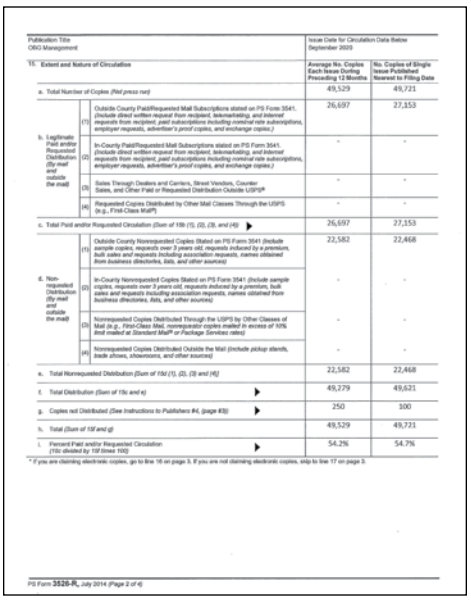

Publication Title: OBG Management
Issue Date for Circulation Data Below: September 2020

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies (Net press run)			49,529	49,721
b. Legitimate Paid and/or Requested Distribution (By mail and outside the mail)	(1)	Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing, and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	26,697	27,153
	(2)	In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing, and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	-	-
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c. Total Paid and/or Requested Circulation (Sum of 15b (1), (2), (3), and (4)) ▶			26,697	27,153
d. Non-requested Distribution (By mail and outside the mail)	(1)	Outside County Nonrequested Copies Stated on PS Form 3541 (Include sample copies, requests over 3 years old, requests induced by a premium, bulk sales and requests including association requests, names obtained from business directories, lists, and other sources)	22,582	22,468
	(2)	In-County Nonrequested Copies Stated on PS Form 3541 (Include sample copies, requests over 3 years old, requests induced by a premium, bulk sales and requests including association requests, names obtained from business directories, lists, and other sources)	-	-
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e. Total Nonrequested Distribution (Sum of 15d (1), (2), (3) and (4))			22,582	22,468
f. Total Distribution (Sum of 15c and e) ▶			49,279	49,621
g. Copies not Distributed (See Instructions to Publishers #4, (page #3)) ▶			250	100
h. Total (Sum of 15f and g)			49,529	49,721
i. Percent Paid and/or Requested Circulation (15c divided by 15f times 100) ▶			54.2%	54.7%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

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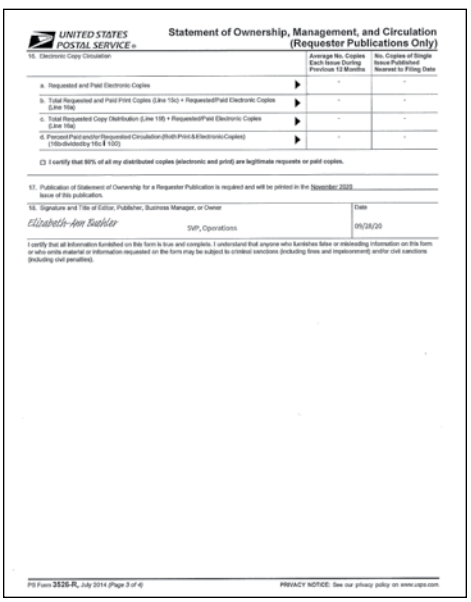

Statement of Ownership, Management, and Circulation (Requester Publications Only)

16. Electronic Copy Circulation	Average No. Copies Each Issue During Previous 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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c. Total Requested Copy Distribution (Line 15f) + Requested/Paid Electronic Copies (Line 16a) ▶	-	-
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17. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the November 2020 issue of this publication.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: Elizabeth-Ann Boehler, SVP, Operations — Date: 09/28/20

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References: 1. Blatt AJ, et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015;123(5):282-288. doi:10.1002/ cncy.21544 (Study included ThinPrep, SurePath and Hybrid Capture 2 assay). **2.** Austin RM, et al. Enhanced detection of cervical cancer and precancer through use of imaged liquid-based cytology in routine cytology and HPV cotesting. Am J Obstet Gynecol. 2018;150(5):385-392. doi:10.1093/ajcp/aqy114 (Study included ThinPrep Pap test, ThinPrep imaging, Digene HPV, Cervista HPV and Aptima HPV).