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OBG MANAGEMENT

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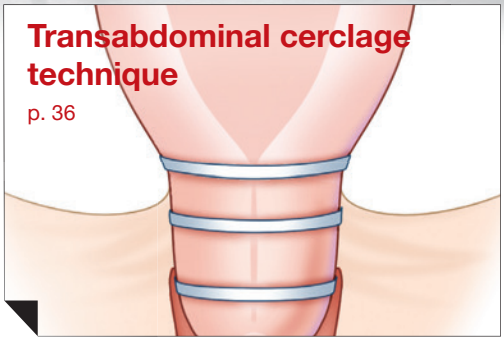


*Statistical significance for dyspareunia was not achieved with the 150 mg QD dose of ORILISSA.

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

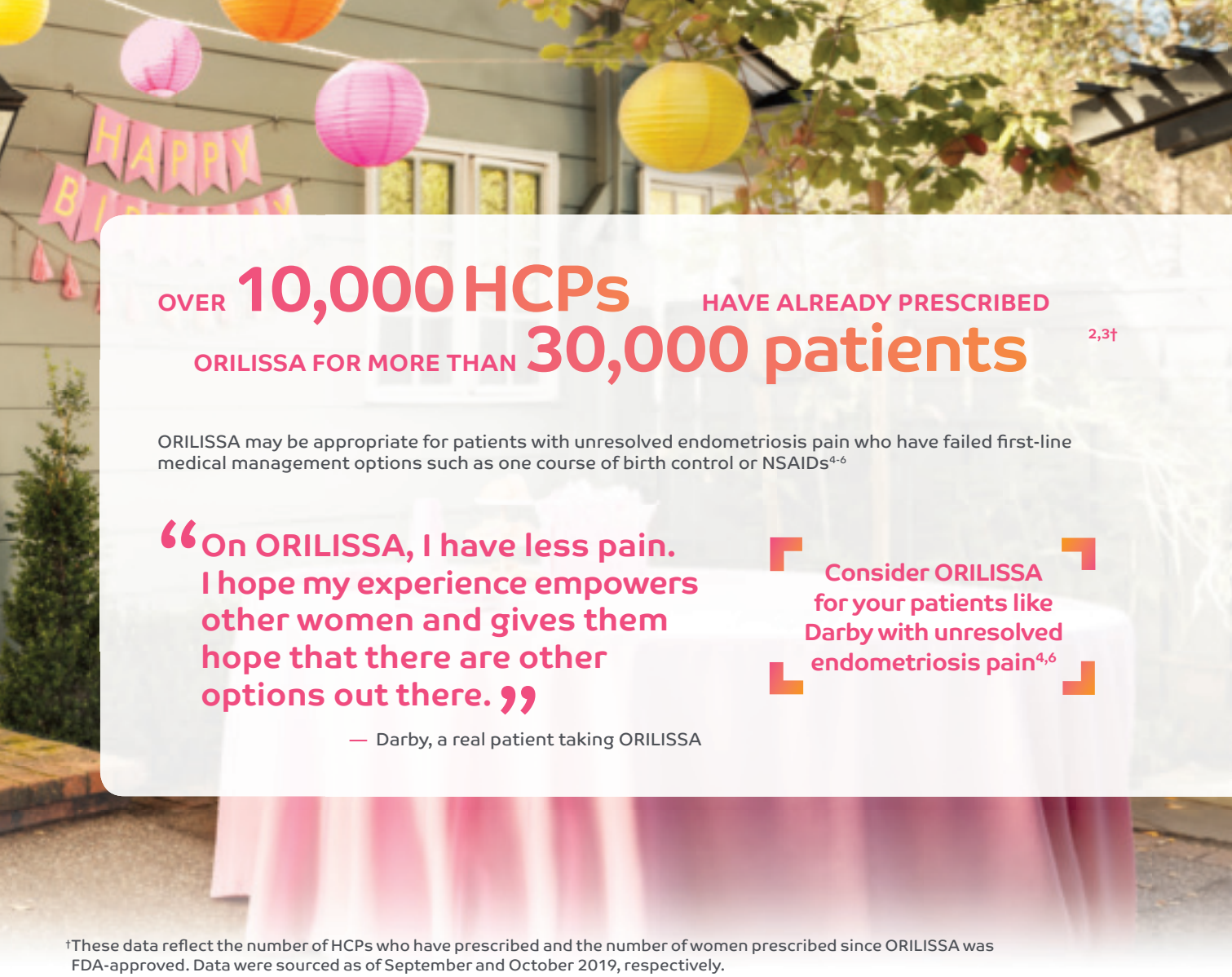
- ORILISSA causes a dose-dependent decrease in bone mineral density (BMD), which is greater with increasing duration of use and may not be completely reversible after stopping treatment.
- The impact of ORILISSA-associated decreases in BMD on long-term bone health and future fracture risk is unknown. 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

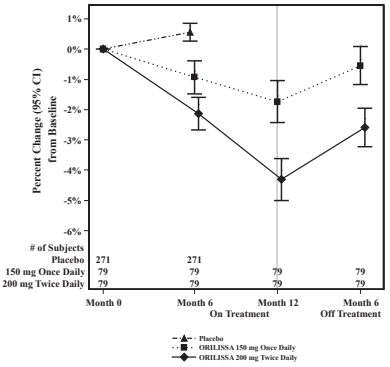
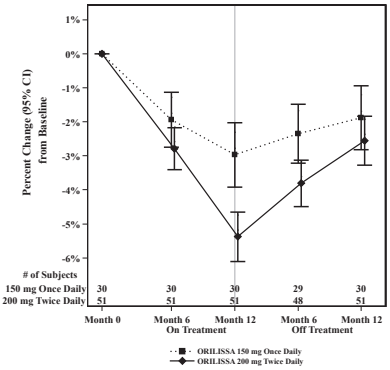


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



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

Adverse Reactions	ORILISSA 150 mg Once Daily (N=475) n (%)	ORILISSA 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.

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Ref: 03-C007 Revised: August, 2019

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

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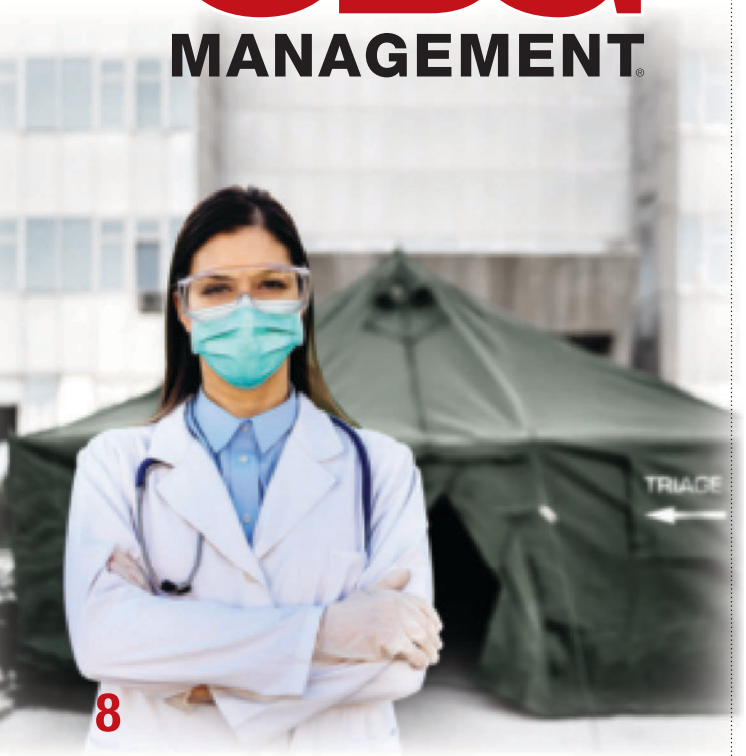

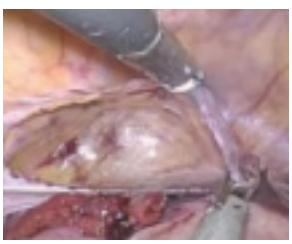

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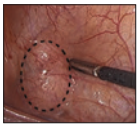

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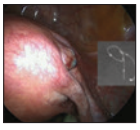

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Host Cara King focuses on COVID-19

See page 43 for more information

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EDITORIAL

COVID-19: We are in a war, without the most effective weapons to fight a novel viral pathogen

Although we are in the midst of battle, we will win this fight, alongside the global community of clinicians

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On June 17, 1775, American colonists, defending a forward redoubt on Breed's Hill, ran out of gunpowder, and their position was overrun by British troops. The Battle of Bunker Hill resulted in the death of 140 colonists and 226 British soldiers, setting the stage for major combat throughout the colonies. American colonists lacked many necessary weapons. They had almost no gunpowder, few field cannons, and no warships. Yet, they fought on with the weapons at hand for 6 long years.

In the spring of 2020, American society has been shaken by the COVID-19 pandemic. Hospitals have been overrun with thousands of people infected with the disease. Some hospitals are breaking under the crush of intensely ill people filling up and spilling out of intensive care units. We are in a war, fighting a viral disease with a limited supply of weapons. We do not have access to the most powerful medical munitions: easily available rapid testing, proven antiviral medications, and an effective vaccine. Nevertheless, clinicians and patients are courageous, and we will continue the fight with the limited weapons we have until the pandemic is brought to an end.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). The virus is aptly named because it is usually transmitted through close contact with *respiratory* droplets. The disease can progress *acutely*, and some people experience a remarkably severe *respiratory syndrome,* including tachypnea, hypoxia, and interstitial and alveolar opacities on chest x-ray, necessitating ventilatory support. The virus is an encapsulated single-stranded RNA virus. When viewed by electron microscopy, the virus appears to have a halo or crown, hence it is named "coronavirus." Among infected individuals, the virus is present in the upper respiratory system and in feces but not in urine.[1] The World Health Organization (WHO) believes that respiratory droplets and contaminated surfaces are the major routes of transmission.[2] The highest risk of developing severe COVID-19 disease occurs in people with one or more of the following characteristics: age greater than 70 years, hypertension, diabetes, respiratory disease, heart disease, and immunosuppression.[3,4] Pregnant women do not appear to be at increased risk for severe COVID-19 disease.[4] The case fatality rate is highest in people 80 years of age or older.[5]

Who is infected with SARS-CoV-2?

Rapid high-fidelity testing for SARS-CoV-2 nucleic acid sequences would be the best approach to identifying people with COVID-19 disease. At the beginning of the pandemic, testing was strictly rationed because of lack of reagents and test swabs. Clinicians were permitted to test only a minority of people who had symptoms. Asymptomatic individuals were not eligible to be tested. This terribly flawed approach to screening permitted a vast army of

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SARS-CoV-2–positive asymptomatic and mildly symptomatic people to circulate unchecked in the general population, infecting dozens of other people, some of whom developed moderate or severe disease. The Centers for Disease Control and Prevention (CDC) has reported on 7 independent clusters of COVID-19 disease, each of which appear to have been caused by one asymptomatic infected individual.[6] Another cluster of COVID-19 disease from China appears to have been caused by one asymptomatic infected individual.[7] Based on limited data, it appears that there may be a 1- to 3-day window where an individual with COVID-19 may be asymptomatic and able to infect others. I suspect that we will soon discover, based on testing for the presence of high-titre anti SARS-CoV-2 antibodies, that many people with no history of illness and people with mild respiratory symptoms had an undiagnosed COVID-19 infection.

As testing capacity expands we likely will be testing all women, including asymptomatic women, before they arrive at the hospital for childbirth or gynecologic surgery, as well as all inpatients and women with respiratory symptoms having an ambulatory encounter.

With expanded testing capability, some pregnant women who were symptomatic and tested positive for SARS-CoV-2 have had sequential long-term follow-up testing. A frequent observation is that over one to two weeks the viral symptoms resolve and the nasopharyngeal test becomes negative for SARS-CoV-2 on multiple sequential tests, only to become positive at a later date. The cause of the positive-negative-negative-positive test results is unknown, but it raises the possibility that once a person tests positive for SARS-CoV-2, they may be able to transmit the infection over many weeks, even after viral symptoms resolve.

COVID-19: Respiratory droplet or aerosol transmission?

Respiratory droplets are large particles (> 5 µm in diameter) that tend

to be pulled to the ground or furniture surfaces by gravity. Respiratory droplets do not circulate in the air for an extended period of time. Droplet nuclei are small particles less than 5 µm in diameter. These small particles may become aerosolized and float through the air for an extended period of time. The CDC and WHO believe that under ordinary conditions, SARS-CoV-2 is transmitted through respiratory droplets and contact routes.[2] In an analysis of more than 75,000 COVID-19 cases in China there were no reports of transmission by aerosolized airborne virus. Therefore, under ordinary conditions, surgical masks, face shields, gowns, and gloves provide a high level of protection from infection.[8]

In contrast to the WHO's perspective, Dr. Harvey Fineberg, Chair of the National Academies of Sciences, Engineering, and Medicine's Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats, wrote a letter to the federal Office of Science and Technology Policy warning that normal breathing might generate aerosolization of the SARS-CoV-2 virus and result in airborne transmission.[9] A report from the University of Nebraska Medical Center supports the concept of airborne transmission of SARS-CoV-2. In a study of 13 patients with COVID-19, room surfaces, toilet facilities, and air had evidence of viral contamination.[10] The investigators concluded that disease spreads through respiratory droplets, person-to-person touch, contaminated surfaces, and airborne routes. Other investigators also have reported that aersolization of SARS-CoV-2 may occur.[11] Professional societies recommend that **all medical staff caring for potential or confirmed COVID-19 patients should use personal protective equipment (PPE), including respirators (N95 respirators) when available.** Importantly, all medical staff should be trained in and adhere to proper donning and doffing of PPE. The controversy about the modes of transmission of SARS-CoV-2 will continue, but as clinicians we need to work within the constraints of the equipment we have.

Certain medical procedures and devices are known to generate aerosolization of respiratory secretions. These procedures and devices include: bronchoscopy, intubation, extubation, cardiopulmonary resuscitation, nebulization, high-flow oxygen masks, and continuous- and bilevel-positive airway pressure devices. When aerosols are generated during the care of a patient with COVID-19, surgical masks are not sufficient protection against infection. When an aerosol is generated maximal protection of health care workers from viral transmission requires use of a negative-pressure room and an N95 respirator or powered air-purifying respirator (PAPR) device. However, negative-pressure rooms, N95 masks, and PAPRs are in very short supply or are unavailable in some health systems. We are lucky at our hospital that all of the labor rooms can be configured to operate in a negative-pressure mode, limiting potential airborne spread of the virus on the unit. Many hospitals restrict the use of N95 masks to anesthesiologists, leaving nurses, ObGyns, and surgical technicians without the best protective equipment, risking their health. As one action to reduce aerosolization of virus, obstetricians can markedly reduce the use of oxygen masks and nasal cannulas by laboring women.

Universal use of surgical masks and mouth-nose coverings

During the entire COVID-19 pandemic, PPE has been in short supply, including severe shortages of N95 masks, PAPRs, and in some health systems, surgical masks, gowns, eye protection, and face shields. Given the severe shortages, some clinicians have needed to conserve PPE, using the same PPE across multiple patient encounters and across multiple work shifts.

Given that the virus is transmitted by respiratory droplets and contaminated surfaces, use of face coverings, including surgical masks, face shields, and gloves is critically important. Scrupulous hand hygiene is a simple approach to reducing infection risk. In my health system, all employees are required to wear a surgical mask, all day every day, requiring distribution of 35,000 masks daily.[12] We also require every patient and visitor to our health care facilities to use a face mask. The purpose of the procedure or surgical mask is to prevent presymptomatic spread of COVID-19 from an asymptomatic health care worker to an uninfected patient or a colleague by reducing the transmission of respiratory droplets. Another benefit is to protect the uninfected health care worker from patients and colleagues who are infected and not yet diagnosed with COVID-19. The CDC now recommends that all people wear a mouth and nose covering when they are outside of their residence. America may become a nation where wearing masks in public becomes a routine practice. Since SARS-CoV-2 is transmitted by respiratory droplets, social distancing is an important preventive measure.

CONTINUED ON PAGE 13

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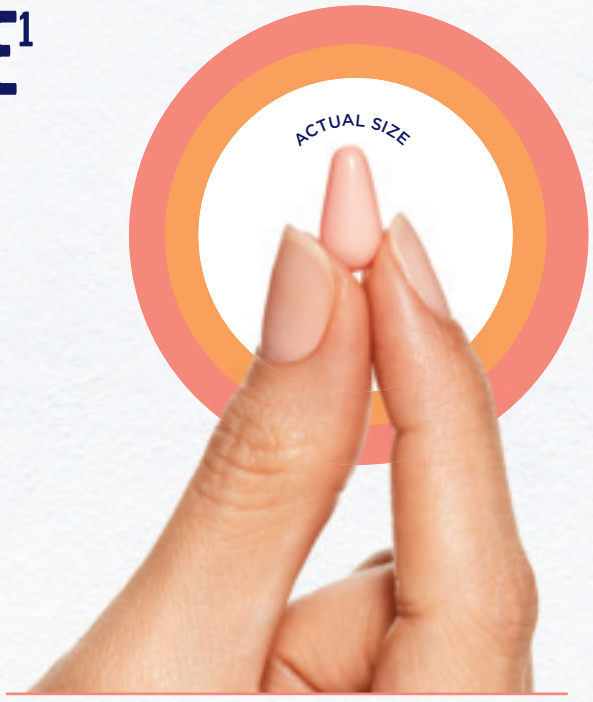

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INDICATION

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

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

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

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

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

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

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

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

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

Cardiovascular Disorders

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

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

Malignant Neoplasms

Endometrial Cancer

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

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

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

Breast Cancer

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

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

Ovarian Cancer

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

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

Probable Dementia

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

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

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

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

Other Warnings and Precautions include:

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Geriatric Use

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

Based on IVXY-LAB-20004.2
Revised: 04/2019

TherapeuticsMD®

IVXY-20054.3 09/2019

CONTINUED FROM PAGE 10

Obstetric care

Can it be repeated too often? No. Containing COVID-19 disease requires social distancing, fastidious hand hygiene, and using a mask that covers the mouth and nose.

Pregnant women should be advised to assiduously practice social distancing and to wear a face covering or mask in public. Hand hygiene should be emphasized. Pregnant women with children should be advised to not allow their children to play with non-cohabiting children because children may be asymptomatic vectors for COVID-19.

Pregnant health care workers should stop face-to-face contact with patients after 36 weeks' gestation to avoid a late pregnancy infection that might cause the mother to be separated from her newborn. Based on data currently available, pregnancy in the absence of another risk factor is not a major risk factor for developing severe COVID-19 disease.[13]

Hyperthermia is a common feature of COVID-19. Acetaminophen is recommended treatment to suppress pyrexia during pregnancy.

The COVID-19 pandemic has transformed prenatal care from a series of face-to-face encounters at a health care facility to telemedicine either by telephone or a videoconferencing portal. Many factors contributed to the rapid switch to telemedicine, including orders by governors to restrict unnecessary travel, patients' fear of contracting COVID-19 at their clinicians' offices, clinicians' fear of contracting COVID-19 from patients, and insurers' rapid implementation of policies to pay for telemedicine visits. Most prenatal visits can be provided through telemedicine as long as the patient has a home blood pressure cuff and can reliably use the instrument. In-person visits may be required for blood testing, ultrasound assessment, anti-Rh immunoglobulin administration, and group B streptococcal infection screening. One regimen is to limit in-person prenatal visits to encounters at 12, 20, 28, and 36 weeks' gestation when blood testing and ultrasound examinations are needed. The postpartum visit also may be conducted using telemedicine.

Pregnant women with COVID-19 and pneumonia are reported to have high rates of preterm birth less than 37 weeks (41%) and preterm prelabor rupture of membranes (19%).[14]

The rate of vertical transmission from mother to fetus is probably very low (<1%).[15] However, based on serological studies, an occasional newborn has been reported to have IgM and IgG antibodies to the SARS-CoV-2 nucleoprotein at birth.[16,17]

Pregnant women should be consistently and regularly screened for symptoms of an upper respiratory infection, including: fever, new cough, new runny nose or nasal congestion, new sore throat, shortness of breath, muscle aches, and anosmia. A report of any of these symptoms should result in nucleic acid testing of a nasal swab for SARS-CoV-2 of all pregnant women. Given limited testing resources, however, symptomatic pregnant women with the following characteristics should be prioritized for testing: if the woman is more than 36 weeks pregnant, intrapartum, or in the hospital after delivery. Ambulatory pregnant women with symptoms who do not need medical care should quarantine themselves at home, if possible, or at another secure location away from their families. In some regions, testing of ambulatory patients with upper respiratory symptoms is limited.

All women scheduled for induction or cesarean delivery (CD) and their support person should have a symptom screen 24 to 48 hours before arrival to the hospital and should be rescreened prior to entry to labor and delivery. In this situation if the pregnant woman screens positive, she should be tested for SARS-CoV-2, and if the test result is positive, the scheduled induction and CD should be rescheduled, if possible. All hospitalized women and their support persons should be screened for symptoms daily. If the pregnant woman screens positive she should have a nucleic acid test for SARS-CoV-2. If the support person screens positive, he or she should be sent home.

Systemic glucocorticoids may worsen the course of COVID-19. For pregnant women with COVID-19 disease, betamethasone administration should be limited to women at high risk for preterm delivery within 7 days and only given to women between 23 weeks to 33 weeks 6 days of gestation. Women at risk for preterm delivery at 34 weeks to 36 weeks and 6 days of gestation should not be given betamethasone.

If cervical ripening is required, outpatient regimens should be prioritized.

One support person plays an important role in optimal labor outcome and should be permitted at the hospital. All support persons should wear a surgical or procedure mask.

Nitrous oxide for labor anesthesia should not be used during the pandemic because it might cause aerosolization of respiratory secretions, endangering health care workers. Neuraxial anesthesia is an optimal approach to labor anesthesia.

Labor management and timing of delivery does not need to be altered during the COVID-19 pandemic. However, pregnant women with moderate or severe COVID-19 disease who are not improving may have a modest improvement in

respiratory function if they are delivered preterm.

At the beginning of the COVID pandemic, the CDC recommended separation of a COVID-positive mother and her newborn until the mother's respiratory symptoms resolved. However, the CDC now recommends that, for a COVID-positive mother, joint decision-making should be used to decide whether to support the baby rooming-in with the mother or to practice separation of mother and baby at birth to reduce the risk for postnatal infection from mother to newborn. There is no evidence that breast milk contains virus that can cause an infection. One option is for the mother who recently tested positive for SARS-CoV-2 to provide newborn nutrition with expressed breast milk.

Pregnant women with COVID-19 may be at increased risk for venous thromboembolism. Some experts recommend that hospitalized pregnant women and postpartum women with COVID-19 receive thromboembolism prophylaxis. The Chinese Centers for Disease Control and Prevention described a classification system for COVID-19 disease, including 3 categories[18]:

- **mild**: no dyspnea, no pneumonia, or mild pneumonia
- **severe**: dyspnea, respiratory frequency ≥ 30 breaths per minute, blood oxygen saturation ≤ 93%, lung infiltrates > 50% within 48 hours of onset of symptoms
- **critical**: respiratory failure, septic shock, or multiple organ dysfunction or failure.

Among 72,314 cases in China, 81% had mild disease, 14% had severe disease, and 5% had critical disease. In a report of 118 pregnant women in China, 92% of the women had mild disease; 8% had severe disease (hypoxemia), one of whom developed critical disease requiring mechanical ventilation.[19] In this cohort, the most common presenting symptoms were fever (75%), cough (73%), chest tightness (18%), fatigue (17%), shortness of breath (7%), diarrhea (7%), and headache (6%). Lymphopenia was present in 44% of the women.

Severe and critical COVID-19 disease are associated with elevations in D-dimer, C-reactive protein, troponin, ferritin, and creatine phosphokinase levels. These markers return to the normal range with resolution of disease.

Gynecologic care

Gynecologists are highly impacted by the COVID-19 pandemic. Most state governments have requested that all elective surgery be suspended for the duration of the pandemic in order to redeploy health resources to the care of COVID-19 patients. Except for high-priority gynecologic surgery, including cancer surgery, treatment of heavy vaginal bleeding, and surgical care of ectopic pregnancy and miscarriage, most gynecologic surgery has ceased.

All office visits for routine gynecologic care have been suspended. Video and telephone visits can be used for contraceptive counseling and prescribing and for managing problems associated with the menopause, endometriosis, and vaginitis. Cervical cancer screening can be deferred for 3 to 6 months, depending on patient risk factors.

Medicines to treat COVID-19 infections

There are many highly effective medicines to manage HIV infection and medicines that cure hepatitis C. There is an urgent need to develop precision medicines to treat this disease. Early in the pandemic some experts thought that hydroxychloroquine might be helpful in the treatment of COVID-19 disease. But recent evidence suggests that hydroxychloroquine is probably not an effective treatment. As the pandemic has evolved, there is evidence that remdesivir may have modest efficacy in treating COVID-19 disease.[20] Remdesivir has received emergency-use authorization by the FDA to treat COVID-19 infection.

Remdesivir

Based on expert opinion, in the absence of high-quality clinical trial evidence, our current practice is to offer pregnant women with severe or critical COVID-19 disease treatment with remdesivir.

Remdesivir (Gilead Sciences, Inc) is a nucleoside analog that inhibits RNA synthesis. A dose regimen for remdesivir is a 200-mg loading dose given intravenously, followed by 100 mg daily given intravenously for 5 to 10 days. Remdesivir may cause elevation of hepatic enzymes. Remdesivir has been administered to a few pregnant women to treat Ebola and Marburg virus disease.[21]

Experts in infectious disease are important resources for determining optimal medication regimens for the treatment of COVID-19 disease in pregnant women.

Convalescent serum

There are no high-quality studies demonstrating the efficacy of convalescent serum for treatment of COVID-19. A small case series suggests that there may be modest benefit to treatment of people with severe COVID-19 disease with convalescent serum.[22]

Testing for anti-SARS-CoV-2 IgM and IgG antibodies

We may have a serious problem in our current approach to detecting

COVID-19 disease. Based on measurement of IgM and IgG antibodies to SARS-CoV-2 nucleocapsid protein, our current nucleic acid tests for SARS-CoV-2 may detect less than 80% of infections early in the course of disease. In two studies of IgM and IgG antibodies to the SARS-CoV-2 nucleocapsid protein, a single polymerase chain reaction test for SARS-CoV-2 had less than a 60% sensitivity for detecting the virus.[23,24] During the second week of COVID-19 illness, IgM or IgG antibodies were detected in greater than 89% of infected patients.[23] Severe disease resulted in high concentrations of antibody.

When testing for IgM and IgG antibodies is widely available, it may become an option to test all health care workers. This will permit the assignment of those health care workers with the highest levels of antibody to frontline duties with COVID-19 patients during the next disease outbreak, likely to occur at some point during the next 12 months.

A COVID-19 vaccine

Dozens of research teams, including pharmaceutical and biotechnology companies and many academic laboratories, are working on developing and testing vaccines to prevent COVID-19 disease. An effective vaccine would reduce the number of people who develop severe disease during the next outbreak, reducing deaths, avoiding a shutdown of the country, and allowing the health systems to function normally. A vaccine is unlikely to be widely available until sometime early in 2021.

Facing COVID-19 well-being and mental health

SARS-CoV-2, like all viral particles, is incredibly small. Remarkably, it has changed permanently life on earth. COVID-19 is affecting our physical health, psychological well-being, economics, and patterns of social interaction. As clinicians it is difficult to face a viral enemy that cannot be stopped from causing the death of more than 100,000 people, including some of our clinical colleagues, within a short period of time.

Dr. Russ Harris, an Australian acceptance commitment therapist, has written an ebook (http://www.commpsych.com/wp-content/uploads/FACE_COVID-1.pdf) and produced an animated YouTube video, titled FACE COVID (https://www.youtube.com/watch?v=BmvNCdpHUYM), which describes a systematic approach to deal with the challenge of the pandemic. He advises a 9-step approach:

- **F**—focus on what is in your control
- **A**—acknowledge your thoughts and feelings
- **C**—come back to a focus on your body
- **E**—engage in what you are doing
- **C**—commit to acting effectively based on your core values
- **O**—opening up to difficult feelings and being kind to yourself and others
- **V**—values should guide your actions
- **I**—identify resources for help, assistance, support, and advice
- **D**—disinfect and practice social distancing.

This war will come to an end

During the American Revolution, colonists faced housing and food insecurity, epidemics of typhus and smallpox, traumatic injury including amputation of limbs, and a complete disruption of normal life activities. They persevered and, against the odds, successfully concluded the war. Unlike the colonists, who did not know if their conflict would end with success or failure, we clinicians know that the COVID-19 pandemic will end. We also know that eventually the global community of clinicians will develop and deploy the effective weapons we need to prevent a recurrence of this traumatic pandemic: population-wide testing for both the SARS-CoV-2 virus and serologic testing for IgG and IgM antibodies to the virus, effective antiviral medications, and a potent vaccine. ●

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

References

1. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens [published online March 11, 2020]. *JAMA*. doi: 10.1001/jama.2020.3786.
2. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. March 29, 2020. https://www.who.int/publications-detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. Accessed April 16, 2020.
3. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State [published online March 19, 2020]. *JAMA*. doi: 10.1001/jama.2020.4326.
4. Guan WJ, Liang WH, Zhao Y, et al; China Medical Treatment Expert Group for Covid-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis [published online March 26, 2020]. *Eur Respir J*. doi: 10.1183/13993003.00547-2020.
5. Onder G, Rezza G, Brusaferro S. Case fatality rate and characteristics of patients dying in relation to COVID-19 in Italy [published online March 23, 2020]. *JAMA*. doi: 10.1001/jama.2020.4683.
6. Wei WE, Li Z, Chiew CJ, et al. Presymptomatic transmission of SARS-CoV-2 - Singapore, January 23 to March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:411-415.
7. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19 [published online February 21, 2020]. *JAMA*. doi: 10.1001/jama.2020.2565.

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Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

SHE MAY SEARCH, BUT YOU ARE HER TRUSTED SOURCE FOR BIRTH CONTROL INFORMATION

NEXPLANON is indicated for use by women to prevent pregnancy.

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.

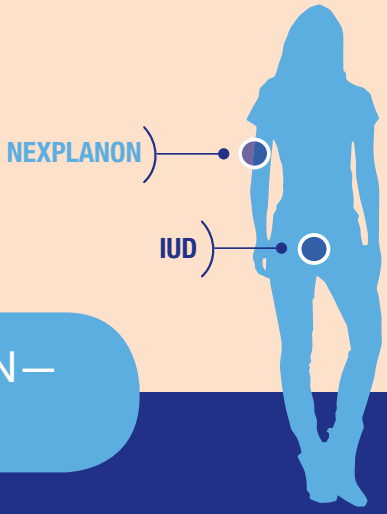
NEXPLANON and pregnancy

- 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.

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For more detailed information, please read the Prescribing Information.
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COMMENTARY

Learning to live with COVID-19: Postpandemic life will be reflected in how effectively we leverage this crisis

Four strategies can help us navigate through the COVID-19 health emergency, and lessons learned can guide thinking on future health care delivery and educational initiatives

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While often compared with the Spanish influenza contagion of 1918, the current COVID-19 pandemic is arguably unprecedented in scale and scope, global reach, and the rate at which it has spread across the world.

Unprecedented times

The United States now has the greatest burden of COVID-19 disease worldwide.[1] Although Boston has thus far been spared the full force of the disease's impact, it is likely only a matter of time before it reaches here. To prepare for the imminent surge, we at Tufts Medical Center defined 4 short-term strategic imperatives to help guide our COVID-19 preparedness. Having a single unified strategy across our organization has helped to maintain focus and consistency in the messaging amidst all of the uncertainty. Our focus areas are outlined below.

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1 Flatten the curve

This term refers to the use of "social distancing" and community isolation measures to keep the number of disease cases at a manageable level. COVID-19 is spread almost exclusively through contact with contaminated respiratory droplets. While several categories of risk have been described, the US Centers for Disease Control and Prevention (CDC) defines disease "exposure" as face-to-face contact within 6 feet of an infected individual for more than 15 minutes without wearing a mask.[2] Intervening at all 3 of these touchpoints effectively reduces transmission. Interventions include limiting in-person meetings, increasing the space between individuals (both providers and patients), and routinely using personal protective equipment (PPE).

Another effective strategy is to divide frontline providers into smaller units or teams to limit cross-contamination: the inpatient team versus the outpatient team, the day team versus the night team, the "on" team versus the "off" team. If the infection lays one team low, other providers can step in until they recover and return to work.

Visitor policies should be developed and strictly implemented. Many institutions do allow one support person in labor and delivery (L&D) regardless of the patient's COVID-19 status, although that person should not be symptomatic or COVID-19 positive. Whether to test all patients and support persons for COVID-19 on arrival at L&D remains controversial.[3] At a minimum, these individuals should be screened for symptoms. Although it was a major focus of initial preventative efforts, taking a travel and exposure history is no longer informative as the virus is now endemic and community spread is common.

Initial preventative efforts focused also on high-risk patients, but routine use of PPE for all encounters clearly is more effective because of the high rate of asymptomatic shedding. The virus can survive suspended in the air for up to 2 hours following an aerosol-generating

procedure (AGP) and on surfaces for several hours or even days. Practices such as regular handwashing, cleaning of exposed work surfaces, and avoiding face touching should by now be part of our everyday routine.

Institutions throughout the United States have established inpatient COVID-19 units—so-called "dirty" units—with mixed success. As the pandemic spreads and the number of patients with asymptomatic shedding increases, it is harder to determine who is and who is not infected. Cross-contamination has rendered this approach largely ineffective. Whether this will change with the introduction of rapid point-of-care testing remains to be seen.

2 Preserve PPE

PPE use is effective in reducing transmission. This includes tier 1 PPE with or without enhanced droplet precaution (surgical mask, eye protection, gloves, yellow gown) and tier 2 PPE (tier 1 plus N95 respirators or powered air-purifying respirators [PAPR]). Given the acute PPE shortage in many parts of the country, appropriate use of PPE is critical to maintain an adequate supply. For example, tier 2 PPE is required only in the setting of an AGP. This includes intubation and, in our determination, the second stage of labor for COVID-19–positive patients and patients under investigation (PUIs); we do not employ tier 2 PPE for all patients in the second stage of labor, although some hospitals endorse this practice.

Creative solutions to the impending PPE shortage abound, such as the use of 3D printers to make face shields and novel techniques to sterilize and reuse N95 respirators.

3 Create capacity

In the absence of effective treatment for COVID-19 and with a vaccine still many months away, supportive care is critical. The pulmonary sequelae with cytokine storm and acute hypoxemia can come on quickly, require urgent mechanical ventilatory support, and take several weeks to resolve.

Our ability to create inpatient capacity to accommodate ill patients, monitor them closely, and intubate early will likely be the most critical driver of the case fatality rate. This requires deferring outpatient visits (or doing them via telemedicine), expanding intensive care unit capabilities (especially ventilator beds), and canceling elective surgeries. What constitutes "elective surgery" is not always clear. Our institution, for example, regards abortion services as essential and not elective, but this is not the case throughout the United States.

Creating capacity also refers to staffing. Where necessary, providers should be retrained and redeployed. This may require emergency credentialing of providers in areas outside their usual clinical practice and permission may be needed from the Accreditation Council for Graduate Medical Education to engage trainees outside their usual duty hours.

4 Support and protect your workforce

Everyone is anxious, and people convey their anxiety in different ways. I have found it helpful to acknowledge those feelings and provide a forum for staff to express and share their anxieties. That said, hospitals are not a democracy. While staff members should be encouraged to ask questions and voice their opinions, everyone is expected to follow protocol regarding patient care.

Celebrating small successes and finding creative ways to alleviate the stress and inject humor can help. Most institutions are using electronic conferencing platforms (such as Zoom or Microsoft Teams) to stay in touch and to continue education initiatives through interactive didactic sessions, grand rounds, morbidity and mortality conferences, and e-journal clubs. These are also a great platform for social events, such as w(h)ine and book clubs and virtual karaoke.

Since many ObGyn providers are women, the closure of day-care centers and schools is particularly challenging. Share best practices among your staff on how to address this problem, such as alternating on-call shifts or matching providers needing day care with "furloughed" college students who are looking to keep busy and make a little money.

Avoid overcommunicating

Clear, concise, and timely communication is key. This can be challenging given the rapidly evolving science of COVID-19 and the daily barrage of information from both reliable and unreliable sources. Setting up regular online meetings with your faculty 2 or 3 times per week can keep people informed, promote engagement, and boost morale.

If an urgent e-mail announcement is needed, keep the message focused. Highlight only updated information and changes to existing policies and guidelines. And consider adding a brief anecdote to illustrate the staff's creativity and resilience: a "best catch" story, for example, or a staff member who started a "commit to sit" program (spending time in the room with patients who want company but are not able to have their family in attendance).

Look to the future

COVID-19 will pass. Herd immunity will inevitably develop. The

question is how quickly and at what cost. Children delivered today are being born into a society already profoundly altered by COVID-19. Some have started to call them Generation C.

Exactly what life will look like at the back end of this pandemic depends on how effectively we leverage this crisis. There are numerous opportunities to change the way we think about health care and educate the next generation of providers. These include increasing the use of telehealth and remote education, redesigning our traditional prenatal care paradigms, and reinforcing the importance of preventive medicine. This is an opportunity to put the "health" back into "health care."

Look after yourself

Amid all the chaos and uncertainty, do not forget to take care of yourself and your family. Be calm, be kind, and be flexible. Stay safe. ●

References

1. Kommenda N, Gutierrez P, Adolphe J. Coronavirus world map: which countries have the most cases and deaths? *The Guardian*. April 1, 2020. https://www.theguardian.com/world/2020/mar/31/coronavirus-mapped-which-countries-have-the-most-cases-and-deaths. Accessed April 1, 2020.
2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Interim US guidance for risk assessment and public health management of healthcare personnel with potential exposure in a healthcare setting to patients with coronavirus disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. Accessed April 1, 2020.
3. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). Evaluating and testing persons for coronavirus disease 2020 (COVID-19). https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html. Accessed April 1, 2020.

EDITORIAL

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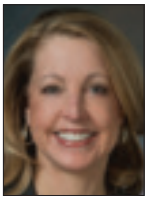
8. Ong SW, Tan YK, Chia PY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient [published online March 4, 2020]. *JAMA*. doi: 10.1001/jama.2020.3227.
9. Fineberg HV. Rapid expert consultation on the possibility of bioaerosol spread of SARS-CoV-2 for the COVID-19 pandemic. April 1, 2020. https://www.nap.edu/read/25769/chapter/1. Accessed April 16, 2020.
10. Santarpia JL, River DN, Herrera V, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. MedRxiv. March 26, 2020. doi.org10.1101/2020.03.23.20039466.
11. Liu Y, Ning Z, Chen Y, et al. Aerodynamic characteristics and RNA concentration of SARS-CoV-2 aerosol in Wuhan Hospitals during COVID-19 outbreak. BioRxiv. March 10, 2020. doi.org/10.1101/2020.03.08.982637.
12. Klompas M, Morris CA, Sinclair J, et al. Universal masking in hospitals in the COVID-19 era [published online April 1, 2020]. *N Engl J Med*. doi: 10.1056/NEJMp2006372.
13. Liu D, Li L, Wu X, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: a preliminary analysis. *AJR Am J Roentgenol*. 2020:1-6. doi: 10.2214/AJR.20.23072.
14. Di Mascio D, Khalik A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID 1-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020:100107. doi:10.1016/j.ajogmf.2020.100107.
15. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens [published online March 11, 2020]. *JAMA*. doi: 10.1001/jama.2020.3786.
16. Dong L, Tian J, He S, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn [published online March 26, 2020]. *JAMA*. doi: 10.1001/jama.2020.4621.
17. Zeng H, Xu C, Fan J, et al. Antibodies in infants born to mothers with COVID-19 pneumonia [published online March 26, 2020]. *JAMA*. doi: 10.1001/jama.2020.4861.
18. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Diease 2019 (COVID-19) outbreak in China. Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention [published online February 24, 2020]. *JAMA*. doi: 10.1001/jama.2020.2648.
19. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with COVID-19 in Wuhan, China [published online April 17, 2020]. *N Engl J Med*. doi 10.1056/NEJMc2009226.
20. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. April 10, 2020. https://doi.org/10.1101/2020.03.22.20040758.
21. Maulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 2019;381:2293-2303.
22. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma [published online March 27, 2020]. *JAMA*. doi: 10.1001/jama.2020.4783.
23. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019 [published online March 29, 2020]. *Clin Infect Dis*. doi: 10.1093/cid/ciaa344.
24. Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19) [published online March 21, 2020]. *Clin Infect Dis*. doi: 10.1093/cid/ciaa310.

COMMENTARY

Steps to leadership during the COVID-19 era and beyond

ObGyn clinical experience and leadership skills can help pilot patient care through the COVID-19 pandemic and plan a cohesive response to future crises



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SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) has challenged us all and will continue to do so for at least the next several months. This novel virus has uncovered our medical hubris and our collective failure to acknowledge our vulnerability in the face of biological threats. As government, public health, health systems, medical professionals, and individuals struggle to grasp its enormous impact, we must recognize and seize the opportunities for leadership that the coronavirus disease (COVID-19) pandemic presents to us as physicians.

For too long we have abdicated responsibility for driving change in the US health system to politicians, administrators, and those not on the front line of care delivery. We can, however, reclaim our voice and position of influence in 2 primary spheres: first, as ObGyns we have the specific clinical knowledge and experience required to help guide our institutions in the care of our patients under new and ever-changing circumstances; second, beyond our clinical role as ObGyns, we are servant leaders to whom the public, the government, our trainees, and our clinical teams turn for guidance.

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Foundations for policy development

Disaster planning in hospitals and public health systems rarely includes consideration for pregnant and delivering patients. As ObGyns, we must create policies and procedures using the best available evidence—which is slim—and, in the absence of evidence, use our clinical and scientific expertise both to optimize patient care and to minimize risk to the health care team.

At this point in time there is much we do not know, such as whether viral particles in blood are contagious, amniotic fluid contains infectious droplets, or newborns are in danger if they room-in with an infected mother. What we do know is that the evidence will evolve and that our policies and procedures must be fluid and allow for rapid change. Here are some guiding principles for such policies.

Maximize telemedicine and remote monitoring

Labor and delivery (L&D) is an emergency department in which people are triaged from the outside. Systems should incorporate the best guidance from the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists while reducing infection exposure to staff, laboring patients and newborns. One way to limit traffic in the triage area is to have a seasoned clinician perform phone triage for women who think they need evaluation for labor.

Maintain universal caution and precautions

All people entering L&D should be presumed to be COVID-19 positive, according to early evidence reported from Columbia University

in New York City.[1] After remote or off-site phone triage determines that evaluation is needed in L&D, a transporter could ensure that all people escorted to L&D undergo a rapid COVID-19 test, wear a mask, and wash their hands. Until point-of-care testing is available, we must adopt safety precautions, since current data suggest that asymptomatic people may shed the infectious virus.

Both vaginal and cesarean deliveries expose everyone in the room to respiratory droplets. Common sense tells us that the laboring patient and her support person should wear a mask and that caregivers should be protected with N95 masks as well as face shields. If this were standard for every laboring patient, exposure during emergency situations might be minimized.

Maximize support during labor

We should not need to ban partners and support people. Solid evidence demonstrates that support in labor improves outcomes, reduces the need for cesarean delivery, and increases patient satisfaction. We can and should protect staff and patients by requiring everyone to wear a mask.

Symptomatic patients, of course, require additional measures and personal protective equipment (PPE) to reduce the risk of infection among the health care team. These should be identical to the measures the hospital infectious disease experts have implemented in the intensive care unit.

Champion continuous quality improvement

It is our responsibility to implement continuous quality improvement processes so that we can respond to data that become available, and this begins with collecting our own local data.

We have sparse data on the risks of miscarriage, congenital anomalies, and preterm birth, but there have been anecdotal reports of both early miscarriage and premature labor. Given the known increased risk for severe disease with influenza during pregnancy, we understandably are concerned about how our pregnant patients will fare. There are also unknowns with respect to fetal exposure risk. During this pandemic we must capture such data within our own systems and share aggregated, de-identified data broadly and swiftly if real signals indicate a need for change in procedures or policy.

In the meantime, we can apply our expertise and best judgment to work within teams that include all stakeholders—administrators, nurses, engineers, pediatricians, infectious disease experts, and public members—to establish policies that respond to the best current evidence.

Protect vulnerable team members

SARS CoV-2 is highly contagious. Thus far, data do not suggest that pregnant women are at higher risk for severe disease, but we must assume that working in the hospital environment among many COVID-19 patients increases the risk for exposure. With so many current unknowns, it may be prudent to keep pregnant health care workers out of clinical areas in the hospital and reassign them to other duties when feasible. Medical students nationwide similarly have been removed from clinical rotations to minimize their exposure risk as well as to preserve scarce PPE.

These decisions are difficult for all involved, and shared decision making between administrators, clinical leaders, and pregnant staff that promotes transparency, honesty, and openness is key. Since the risk is unknown and financial consequences may result for both the hospital and the staff member, open discussion and thoughtful policies that can be revised as new information is obtained will help achieve the best possible resolution to a difficult situation.

ObGyns as servant leaders

COVID-19 challenges us to balance individual and public health considerations while also considering the economic and social consequences of actions. The emergence of this novel pathogen and its rapid global spread are frightening both to an uninformed public and to our skeptical government officials. Beyond our immediate clinical responsibilities, how should we as knowledgeable professionals respond?

Servant leaders commit to service and support and mentor those around them with empathy and collaboration. Servant leaders have the strategic vision to continuously grow, change, and improve at all times, but especially during a crisis. COVID-19 challenges us to be those servant leaders. To do so we must:

Promote and exhibit transparency by speaking truth to power and communicating with empathy for patients, staff, and those on the front lines who daily place themselves and their families at risk to ensure that we have essential services. Amplifying the needs and concerns of the frontline workers can drive those in power to develop practical and useful solutions.

Nurses and physicians have been threatened, and some actually terminated from their positions, because they publicly disclosed their institutions' working conditions, lack of PPE, and unpreparedness. For example, a decorated US Navy captain

was stripped of his command for writing a letter to drive action in managing a COVID-19 outbreak on the confined quarters of his ship. Such public health heroes have exhibited professionalism and leadership, placing the health and well-being of their colleagues, peers, and patients above their own careers. If we all spoke up with honesty and openness, we could have profound impact.

Hold ourselves and others accountable for scientific rigor and honesty. We must acknowledge what we do not know and be straightforward in discussing risks and benefits. The uncertainty surrounding the COVID-19 public health crisis has created anxiety among health care workers, public-facing workers, government officials, and the public. We should not speculate but rather speak clearly and openly about our knowledge deficits.

The US culture in health care drives us to prefer action over inaction. "Doing something" feels proactive, and we are conditioned to think of doing something as a less risky strategy than watchful waiting. In this time of uncertainty, we must be wary of unproven and potentially harmful interventions, and we must use our best judgment and expertise to study procedures and medications that have potential benefit.

Be collaborative and creative in crafting practical workarounds that can be implemented at scale. New processes implemented in the past month to accommodate our new socially and physically distant reality include telemedicine for prenatal care, home monitoring of blood pressure, remote physiologic monitoring of blood sugars for diabetic patients, reviewing digital images to provide remote wound care, and home pulse oximetry to assess COVID-19–positive patients at home.

More workarounds are needed to support women's ongoing health needs. Our expertise should guide those strategies while we strive to optimize outcomes, minimize resource utilization, and reduce exposure risk for ourselves, our staff, and our patients.

Advocate for systems to collect and analyze robust data so we can adjust interventions rapidly as new information arises. As we navigate the pandemic, the lack of evidence to inform decisions and treatment challenges us daily. We should use the current crisis to promote strategies that will support rapid, comprehensive data collection during disasters. Knowledge truly is power, and without it we are forced to improvise and speculate.

ObGyns must insist that data collection includes all pregnancies—not only those positive for COVID-19 since the testing has been sporadic and imperfect—and that the data are stratified by age, gender, race and ethnicity, and sociodemographics. This would enable us to learn as much as possible as quickly as possible and would therefore inform our responses for the current SARS CoV-2 pandemic as well as for the next disaster.

Acknowledge the limitations of the system and be wise stewards of resources. Our health care system does not have sufficient resources to manage patients with severe COVID-19 and the "usual" emergencies like stroke, myocardial infarction, ectopic pregnancy, and broken bones.

Disaster planning should include a regional triage system that can take incoming calls and direct emergency medical technicians, ambulances, and private citizens to appropriate facilities and direct those who do not require urgent medical care away from those facilities.

We must incorporate principles from battlefield medicine, because this is a battle, and we are at war. That means there will be difficult decisions. It is better to engage a regional team of experts to create a system for triage and care delivery than for each provider and institution to be forced by a void in leadership to go it individually. We should engage with government and public health officials to optimize both cure and care. Although we are unable to save everyone, we can work to ensure comfort and care for all.

Demonstrate compassion and caring for patients and each other. During the COVID-19 pandemic crisis, we can each channel our best selves to support and protect each other physically and emotionally. Many of us chose ObGyn because it is generally a "happy" specialty. None of us entered medicine to watch people die or to be unable to comfort them, to be unable to allow their families to be with them, to be unable to "do something."

A crucial part of disaster planning and response is to prepare for the second victims: those of us forced to keep going through our emotional distress because there is no time to debrief and process our pain. Frontline caregivers need support and help now as well as after the surge passes. We need to speak up to ensure there is adequate PPE, creative staffing, and supportive resources to help caregivers process their anxiety, fatigue, and distress.

Take the lead

Every crisis brings both risk and opportunity. The COVID-19 pandemic provides ObGyns the chance to have a louder voice and a meaningful seat at the table as new and creative policies must be implemented at every level. We can use this opportunity

to recapture our roles as champions for women and leaders within our health care system.

Critical steps in servant leadership include speaking up with honesty, transparency, and openness; taking risks to disclose inequities, dangerous conditions, and inadequate resources; and committing ourselves to each other, our teams, and the public. When we take these steps, we will be the driving force for a cohesive, reasoned, structured, and compassionate response to the COVID-19 crisis. As we seize this opportunity to lead, we will rekindle our passion for medicine, caring for the sick, and protecting the well. ●

Reference

1. Sutton D, Fuchs K, D'Alton M, et al. Universal screening for SARS-CoV-2 in women admitted for delivery [letter]. *N Engl J Med.* April 13, 2020. doi:10.1056/NEJMc2009316.

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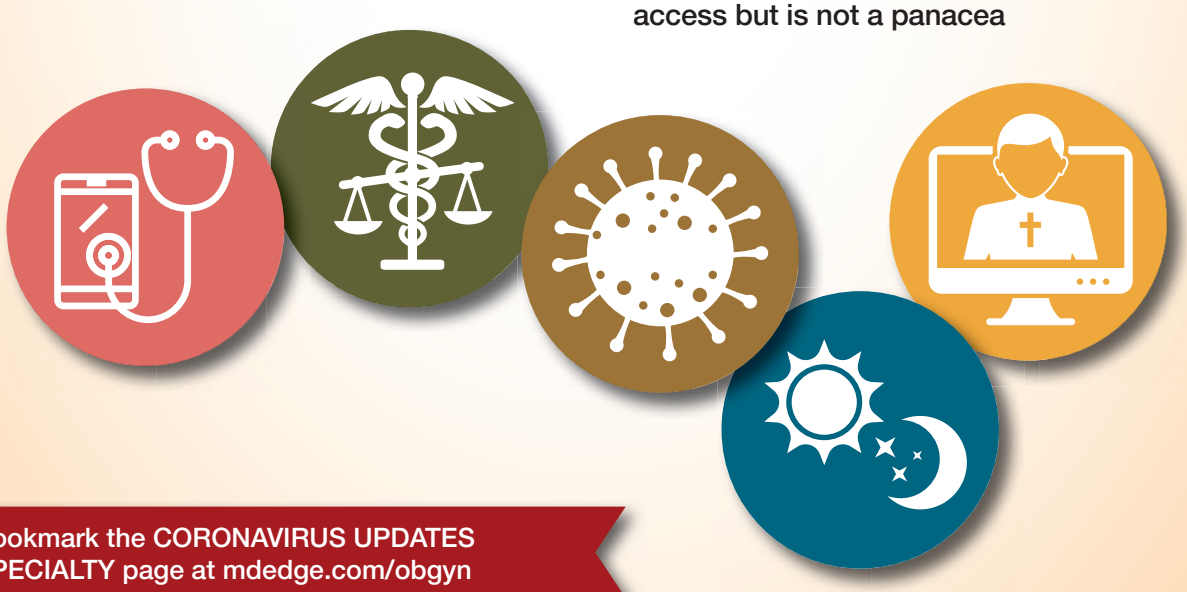

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PART 1 OF 3

Telemedicine: A primer for today's ObGyn

Ready or not, you should be embracing the technology. Here's how to get started.

Mickey Karram, MD, and Neil Baum, MD

IN THIS ARTICLE

If telemedicine had not yet begun to play a significant role in your ObGyn practice, it is almost certain to now as the COVID-19 pandemic demands new ways of caring for our patients while keeping others safe from disease. According to the American College of Obstetricians and Gynecologists (ACOG), the term "telemedicine" refers to delivering traditional clinical diagnosis and monitoring via technology (see "ACOG weighs in on telehealth," page 31).[1]

Whether they realize it or not, most ObGyns have practiced a simple form of telemedicine when they take phone calls from patients who are seeking medication refills. In these cases, physicians either can call the pharmacy to refill the medication or suggest patients make an office appointment to receive a new prescription (much to the chagrin of many patients—especially millennials). Physicians who acquiesce to patients' phone requests to have prescriptions filled or to others seeking free medical advice are not compensated for these services, yet are legally responsible for their actions and advice—a situation that does not make for good medicine.

This is where telemedicine can be an important addition to an ObGyn practice. Telemedicine saves the patient the time and effort of coming to the office, while providing compensation to the physician for his/her time and advice and providing a record of the interaction, all of which makes for far better medicine. This article—the first of 3 on the subject—discusses the process of integrating telemedicine into a practice with minimal time, energy, and expense.

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Telemedicine and the ObGyn practice

Many ObGyn patients do not require an in-person visit in order to receive effective care. There is even the potential to provide prenatal care via telemedicine by replacing some of the many prenatal well-care office visits with at-home care for pregnant women with low-risk pregnancies. A typical virtual visit for a low-risk pregnancy includes utilizing home monitoring equipment to track fetal heart rate, maternal blood pressure, and fundal height.[2]

Practices typically use telemedicine platforms to manage one or both of the following

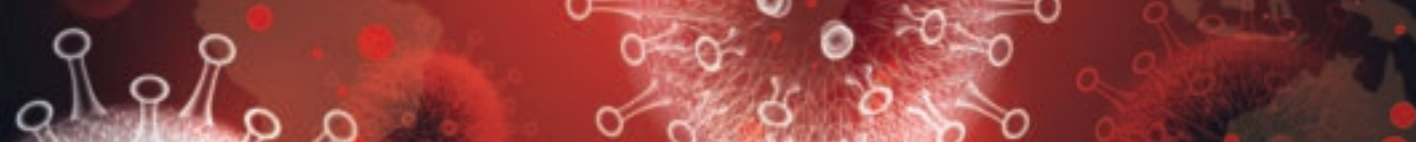

TABLE 1 Sample telemedicine video conferencing products

Products	Pros	Cons
Google+ Hangout	Free	No screen sharing
SecureVideo	HIPAA compliant	
Skype	Market leader for voice and video	No screen sharing Requires ample bandwidth Not encrypted or HIPAA compliant
Tango	Excellent on iPhone, Android	No screen sharing
WebEx	Leader for presentation/webinars	Decreased video performance
Zoom	Mobile support iPad, iPhone, Android	Group video not free after 40 minutes
CiscoJabber	Supported on all mobile devices (iPad, iPhone, Blackberry, Android)	Complicated server requirements and difficult to cross firewalls

Abbreviation: HIPAA, Health Insurance Portability and Accountability Act.

types of encounters: 1) walk-in visits through the practice's web site; for most of these, patients tend not to care which physicians they see; their priority is usually the first available provider; and 2) appointment-based consultations, where patients schedule video chats in advance, usually with a specific provider.

Although incorporating telemedicine into a practice may seem overwhelming, it requires minimal additional equipment, interfaces easily with a practice's web site and electronic medical record (EMR) system, increases productivity, and improves workflow. And patients generally appreciate the option of not having to travel to the office for an appointment.

Most patients and physicians are already comfortable with their mobile phones, tablets, social media, and wearable technology, such as Fitbits. Telemedicine is a logical next step. And given the current situation with COVID-19, it is really not a matter of "if," but rather "when" to incorporate telemedicine as a communication and practice tool, and the sooner the better.

Getting started

Physicians and their colleagues and staff first need to become comfortable with telemedicine technology. Physicians can begin by using video communication for other purposes, such as for conducting staff meetings. They should practice starting and ending calls and adjusting audio volume and video quality to ensure good reception.

Selecting a video platform

TABLE 1 provides a list of the most popular video providers and the advantages and disadvantages of each, and **TABLE 2** shows a list of free video chat apps. Apps are available that can:

- share and mark up lab tests, magnetic resonance images, and other medical documents without exposing the entire desktop
- securely send documents over a Health Insurance Portability and Accountability Act (HIPAA)-compliant video
- stream digital device images live while still seeing patients' faces.

Physicians should make sure their implementation team has the necessary equipment, including webcams, microphones, and speakers, and they should take the time to do research and test out a few programs before selecting one for their practice. Consider appointing a telemedicine point person who is knowledgeable about the technology and can patiently explain it to others. And keep

TABLE 2 Example telemedicine apps

• Amwell
• Babylon (translation software)
• Dialogue
• Doctor on Demand
• First Opinion
• HealthTap
• Lemonaid
• MDLive
• Pager
• PlushCare

in mind that video chatting is dependent upon a fast, strong Internet connection that has sufficient bandwidth to transport a large amount of data. If your practice has connectivity problems, consider consulting with an information technology (IT) expert.

Testing it out and obtaining feedback

Once a team is comfortable using video within the practice, it is time to test it out with a few patients and perhaps a few payers. Most patients are eager to start using video for their medical encounters. Even senior patients are often willing to try consults via video. According to a recent survey, 64% of patients are willing to see a physician over video.[3] And among those who were comfortable accepting an invitation to participate in a video encounter, increasing age was actually associated with a higher likelihood to accept an invite.

Physician colleagues, medical assistants, and nurse practitioners will need some basic telemedicine skills, and physicians and staff should be prepared to make video connections seamless for patients. Usually, patients need some guidance and encouragement, such as telling them to check their spam folder for their invites if the invites fail to arrive in their email inbox, adjusting audio settings, or setting up a webcam. In the beginning, ObGyns should make sure they build in plenty of buffer time for the unexpected, as there will certainly be some "bugs" that need to be worked out.

ObGyns should encourage and collect patient feedback to such questions as:

- What kinds of devices (laptop, mobile) do they prefer using?
- What kind of networks are they using (3G, corporate, home)?
- What features do they like? What features do they have a hard time finding?
- What do they like or not like about the video experience?
- Keep track of the types of questions patients ask, and be patient as patients become acclimated to the video consultation experience.

Streamling online workflow

Armed with feedback from patients, it is time to start streamlining online workflow. Most ObGyns want to be able to manage video visits in a way that is similar to the way they manage face-to-face visits with patients. This may mean experimenting with a virtual waiting room. A virtual waiting room is a simple web page or link that can be sent to patients. On that page, patients sign in with minimal demographic information and select one of the time slots when the physician is available. Typically, these programs are designed to alert the physicians and/or staff when a patient enters the virtual waiting room. Patients have access to the online patient queue and can start a chat or video call when both parties are ready. Such a waiting room model serves as a stepping stone for new practices to familiarize themselves with video conferencing. This approach is also perfect for practices that already have a practice management system and just want to add a video component.

Influences on practice workflow

With good time management, telemedicine can improve the efficiency and productivity of your practice. Your daily schedule and management of patients will need some minor changes, but significant alterations to

your existing schedule and workflow are generally unnecessary. One of the advantages of telemedicine is the convenience of prompt care and the easy access patients have to your practice. This decreases visits to the emergency department and to urgent care centers.

Consider scheduling telemedicine appointments at the end of the day when your staff has left the office, as no staff members are required for a telemedicine visit. Ideally, you should offer a set time to communicate with patients, as this avoids having to make multiple calls to reach a patient. Another advantage of telemedicine is that you can provide care in the evenings and on weekends if you want. Whereas before you might have been fielding calls from patients during these times and not being compensated, with telemedicine you can conduct a virtual visit from any location and any computer or mobile phone and receive remuneration for your care.

And while access to care has been a problem in many ObGyn practices, many additional patients can be accommodated into a busy ObGyn practice by using telemedicine.

Telemedicine and the coronavirus

The current health care crisis makes implementing telemedicine essential. Patients who think they may have COVID-19 or who have been diagnosed need to be quarantined. Such patients can be helped safely in the comfort of their own homes without endangering others. Patients can be triaged virtually. All those who are febrile or have respiratory symptoms can continue to avail themselves of virtual visits.

According to reports in the media, COVID-19 is stretching the health care workforce to its limits and creating a shortage, both because of the sheer number of cases and because health care workers are getting sick themselves. Physicians who test positive do not have to be completely removed from the workforce if they have the ability to care for patients remotely from their homes. And not incidentally the new environment has prompted the Centers for Medicaid and Medicare Services (CMS) and private payers to initiate national payment policies that create parity between office and telemedicine visits.[4]

Bottom line

Patient-driven care is the future, and telemedicine is part of that. Patients want to have ready access to their health care providers without having to devote hours to a medical encounter that could be completed in a matter of minutes via telemedicine.

In the next article in this series, we will review the proper coding for a telemedicine visit so that appropriate compensation is gleaned. We will also review the barriers to implementing telemedicine visits. The

ACOG weighs in on telehealth

The American College of Obstetricians and Gynecologists (ACOG) encourages all practices and facilities without telemedicine capabilities "to strategize about how telehealth could be integrated into their services as appropriate."[1] In doing so, they also encourage consideration of ways to care for those who may not have access to such technology or who do not know how to use it.

They also explain that a number of federal telehealth policy changes have been made in response to the COVID-19 pandemic, and that most private health insurers are following suit.[2] Such changes include:

- covering all telehealth visits for all traditional Medicare beneficiaries regardless of geographic location or originating site
- not requiring physicians to have a pre-existing relationship with a patient to provide a telehealth visit
- permitting the use of FaceTime, Skype, and other everyday communication technologies to provide telehealth visits.

A summary of the major telehealth policy changes, as well as information on how to code and bill for telehealth visits can be found at https://www.acog.org/clinical-information/physician-faqs/~/link.aspx?_id=3803296EAAD940C69525D4DD2679A00E&_z=z.

References

1. American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, gynecology. https://www.acog.org/clinical-information/physician-faqs/covid19-faqs-for-ob-gyns-gynecology. Accessed April 8, 2020.
2. American College of Obstetricians and Gynecologists. Managing patients remotely: billing for digital and telehealth services. Updated April 2, 2020. https://www.acog.org/clinical-information/physician-faqs/~/link.aspx?_id=3803296EAAD940C69525D4DD2679A00E&_z=z. Accessed April 8, 2020.

third article is written with the assistance of 2 health care attorneys, Anjali Dooley and Nadia de la Houssaye, who are experts in telemedicine and who have helped dozens of practices and hospitals implement the technology. They provide legal guidelines for ObGyns who are considering adding telemedicine to their practice. ●

References

1. Implementing telehealth in practice. ACOG Committee Opinion. February 2020. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/02/implementing-telehealth-in-practice. Accessed April 6, 2020.
2. de Mooij MJM, Hodny RL, O'Neil DA, et al. OB nest: reimagining low-risk prenatal care. *Mayo Clin Proc.* 2018;93:458-466.
3. Gardner MR, Jenkins SM, O'Neil DA, et al. Perceptions of video-based appointments from the patient's home: a patient survey. *Telemed J E Health.* 2015;21:281-285.
4. American College of Obstetricians and Gynecologists. Managing patients remotely: billing for digital and telehealth services. Updated April 2, 2020. https://www.acog.org/clinical-information/physician-faqs/~/link.aspx?_id=3803296EAAD940C69525D4DD2679A00E&_z=z. Accessed April 8, 2020.

A multicenter RCT makes a case for transabdominal cerclage

According to results of a recent trial, transabdominal cerclage should be considered the treatment of choice for women with a prior failed transvaginal cerclage, but the risks also must be weighed

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Since the 1950s, when Shirodkar (1955) and McDonald (1957) published their seminal works detailing a transvaginal method to suture a "weak" cervix, clinicians and researchers have debated the indications for and utility of cerclage for preventing pregnancy loss and preterm birth.[1,2]

Originally based on a history of recurrent mid-trimester loss (that is, a clinical diagnosis of cervical insufficiency), cerclage has been expanded to capture both ultrasonography and physical-exam indications. While cerclage has proven useful in select patient populations, an infrequent but vexing problem is what to do when a woman has experienced 1 or more (transvaginal) cerclage "failures."

With a dearth of well-controlled, randomized data to support the use of cerclage for either history- or physical-exam indications, it is not surprising that we still debate whether the Shirodkar method is superior to the McDonald technique as well as how to best manage a patient when either or both methods previously resulted in an unsatisfactory outcome.

The author reports no financial relationships relevant to this article.

First randomized study to directly compare cerclage techniques

Fortunately, Shennan and colleagues in the United Kingdom have greatly enlarged our knowledge in this area by performing the first well-powered, 3-arm, randomized trial of transabdominal cerclage (TAC) compared with both high and low vaginal cerclage (HVC, LVC).[3] They analyzed data for 111 women who were randomly assigned to TAC (n = 39), HVC (n = 39), or LVC (n = 33).

Interestingly, the investigators chose to not attach conventional eponymous labels to their transvaginal methods, and they do not even provide a reference or detailed description of the surgical methods, telling us instead that, "Techniques used were left to the local clinician's discretion." Writing also that HVC cases, like the transabdominal surgeries, were carried out in specialty centers, they implied that additional training was required for the HVC. I inferred that indeed they actually were performing the McDonald and Shirodkar transvaginal methods and with possible by-physician, local modifications.

I am certain that the authors' results did not surprise proponents of transabdominal cerclage for transvaginal cerclage failures, defined in this trial as prior birth from 14 to 28 weeks' gestation. Since some clinicians use a more generous definition of cerclage failure (such as birth at less than 34 weeks), this study population was clearly at high risk for poor outcomes; in fact, more than 90% of each group had experienced at least 2 prior mid-trimester losses. As anticipated with randomization, other characteristics were well distributed across the 3 groups.

Transabdominal cerclage significantly reduced preterm birth rates

Using a primary outcome of preterm birth less than 32 weeks,

which concentrates neonatal morbidities, the investigators observed an overall 4.5-fold higher rate of preterm birth in the transvaginal cohorts compared with the transabdominal patients (33% and 38% versus 8%, respectively). Comparing the TAC group individually with both LVC and HVC groups, the relative risk of preterm birth was 0.20 compared with the HVC group and 0.23 compared with the LVC group, reflecting an approximate 80% reduction.

Not surprising to me, the investigators observed nearly identical outcomes between the HVC and LVC cohorts, substantiating *my* bias that the 2 transvaginal methods are similarly effective. Opponents will quickly remind me that the study was not well-powered to detect a clinically significant difference between these 2 groups; touché!

Risks of TAC. We all know that, despite its now-proven benefits, the transabdominal approach is associated with a risk of special complications, including the surgical risks of placement (and removal) of the cerclage, the management of fetal death beyond approximately 14 weeks, and the absolute requisite for hysterotomy/cesarean birth. While serious complications are rare, in the trial by Shennan and colleagues none were recorded in the 39 TAC cases. Nevertheless, for women with no children or only prior early births, the risks seem to be justified; the number needed to treat was less than 4 to prevent 1 birth at less than 32 weeks and was 5.3 to prevent a fetal loss.

TAC is an option for select patients

Given that TAC now can be successfully placed using minimally invasive surgery, either prior to or following conception, this study provides unique level I evidence that should not be discounted and should further be considered in the context of confirming prior cohort studies that suggested a significant benefit. Although specialized training is required and the procedure may involve travel to a specialty center, the weight of clinical data clearly supports the use of TAC.

In summary, based largely on the trial by Shennan and colleagues, women with prior failed vaginal cerclage can and should be counseled regarding the availability of TAC and given the opportunity to weigh the reported risks and benefits. ●

References

1. Shirodkar VN. A new method of operative treatment for habitual abortion in the second trimester of pregnancy. *Antiseptic.* 1955;52:299-303.
2. McDonald IA. Suture of the cervix for inevitable miscarriage. *J Obstet Gynecol Br Emp.* 1957;64:346-350.
3. Shennan A, Chandiramani M, Bennett P, et al. MAVRIC: a multicenter randomized trial of transabdominal vs transvaginal cervical cerclage. *Am J Obstet Gynecol.* 2020;222:261.e1-261.e9.

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Transabdominal cerclage for managing recurrent pregnancy loss

Among women in whom prior transvaginal cerclage has failed, transabdominal cerclage has a high rate of success in providing a good pregnancy outcome

Eric G. Crihfield, MD; Renae Shibata, MD; Olivia Moskowitz, MD; Gianni Rodriguez-Ayala, MD; and Michael L. Nimaroff, MD

IN THIS ARTICLE

CASE A woman with recurrent pregnancy loss

A 38-year-old woman (G4P0221) presents to your office for preconception counseling. Her history is significant for the following: a spontaneous pregnancy loss at 15 weeks' gestation; a pregnancy loss at 17 weeks secondary to preterm premature rupture of membranes (PPROM); a cesarean delivery at 30 weeks and 6 days' gestation after placement of a transvaginal cerclage at 20 weeks for cervical dilation noted on physical exam (the child now has developmental delays); and most recently a delivery at 24 weeks and 4 days due to preterm labor with subsequent neonatal demise (this followed a transvaginal cerclage placed at 13 weeks and 6 days).

How would you counsel this patient?

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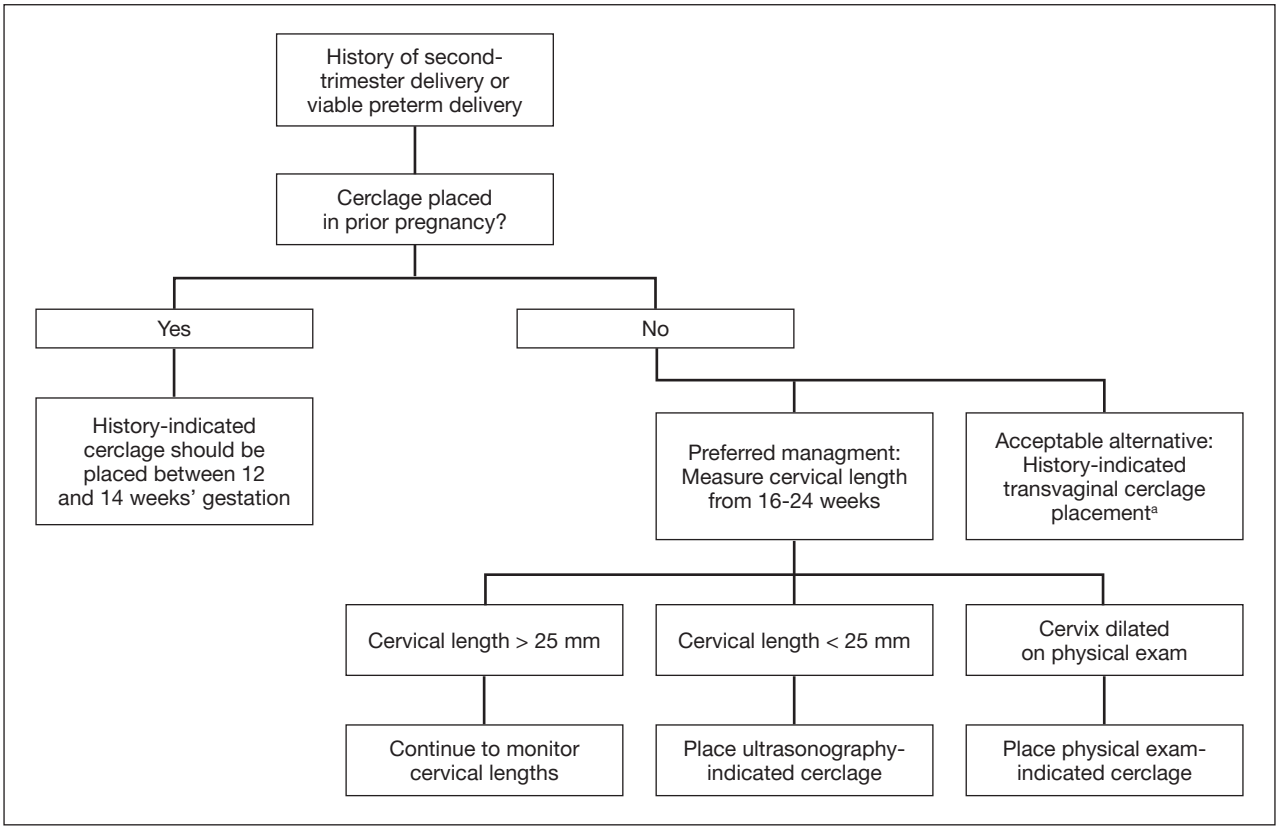
Cervical insufficiency describes the inability of the cervix to retain a pregnancy in the absence of the signs and symptoms of clinical contractions, labor, or both in the second trimester.[1] This condition affects an estimated 1% of obstetric patients and 8% of women with recurrent losses who have experienced a second-trimester loss.[2]

Diagnosis of cervical insufficiency is based on a history of painless cervical dilation after the first trimester with expulsion of the pregnancy in the second trimester before 24 weeks of gestation without contractions and in the absence of other pathology, such as bleeding, infection, or ruptured membranes.[1] Diagnosis also can be made by noting cervical dilation on physical exam during the second trimester; more recently, short cervical length on transvaginal ultrasonography in the second trimester has been used to try to predict when a cervical cerclage may be indicated, although sonographic cervical length is more a marker for risk of preterm birth than for cervical insufficiency specifically.[1,3]

Given the considerable emotional and physical distress that patients experience with recurrent second-trimester losses and the significant neonatal morbidity and mortality that can occur with preterm delivery, substantial efforts are made to prevent these outcomes by treating patients with cervical insufficiency and those at risk for preterm delivery.

FIGURE 1 Decision tree for placement of transvaginal cerclage[1]



[a]According to the American College of Obstetricians and Gynecologists, history-indicated transvaginal cerclage can be placed in the case of a history of 1 or more second-trimester pregnancy losses related to painless cervical dilation even if no cerclage was placed in a prior pregnancy; however, more recently, tracking cervical length has become preferred management as it avoids unnecessary cerclage in one-half of patients.[1]

Transvaginal cerclage: A treatment mainstay

Standard treatment options for cervical insufficiency depend on the patient's history. One of the treatment mainstays for women with prior second-trimester losses or preterm deliveries is transvaginal cervical cerclage. A transvaginal cerclage can be placed using either a Shirodkar technique, in which the vesicocervical mucosa is dissected and a suture is placed as close to the internal cervical os as possible, or a McDonald technique, in which a purse-string suture is placed around the cervicovaginal junction. No randomized trials have compared the effectiveness of these 2 methods, but most observational studies show no difference, and one suggests that the Shirodkar technique may be more effective in obese women specifically.[4-6]

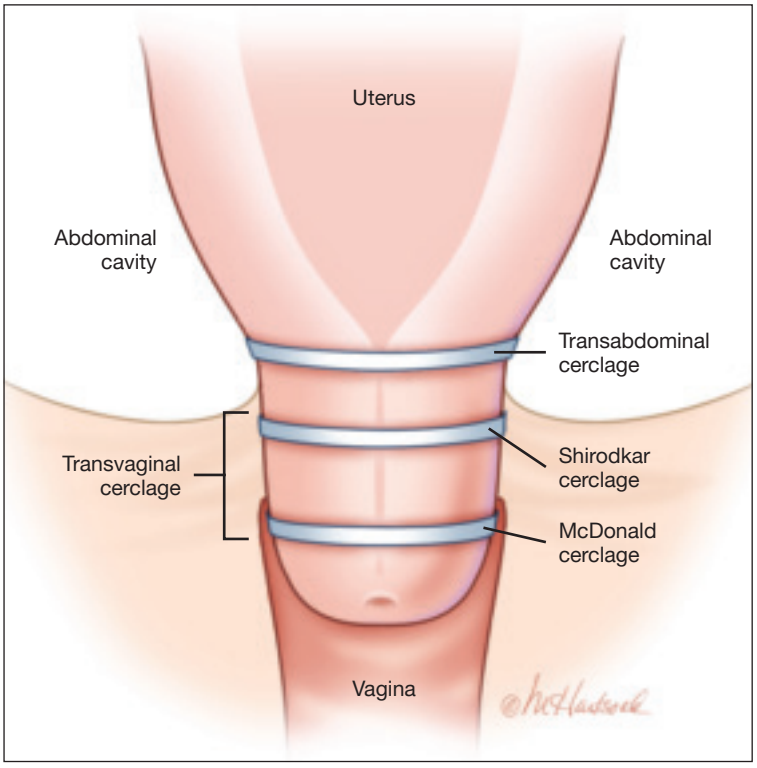
Indications for transvaginal cerclage. The indication for transvaginal cerclage is based on history, physical exam, or ultrasonography.

A physical-exam indication is the most straightforward of the 3. Transvaginal cerclage placement is indicated if on physical exam in the second trimester a patient has cervical dilation without contractions or infection.[1,7]

A history-indicated cerclage (typically placed between 12 and 14 weeks' gestation) is based on a cerclage having been placed in a prior pregnancy due to painless cervical dilation in the second trimester (either ultrasonography- or physical-exam indicated), and it also can be considered in the case of a history of 1 or more second-trimester pregnancy losses related to painless cervical dilation.[1]

More recent evidence suggests that in patients with 1 prior second-trimester loss or

FIGURE 2 Suture placement in transvaginal and transabdominal cerclage procedures



preterm delivery, serial sonographic cervical length can be measured safely from 16 to 24 weeks, with a cerclage being placed only if cervical length decreases to less than 25 mm. By using the ultrasonography-based indication, unnecessary history-indicated cerclages for 1 prior second-trimester or preterm birth can be avoided in more than one-half of patients (**FIGURE 1,** page 37).[1,7]

Efficacy. The effectiveness of transvaginal cerclage varies by the indication. Authors of a 2017 Cochrane review found an overall reduced risk of giving birth before 34 weeks' gestation for any indication, with an average relative risk of 0.77.[2] Other recent studies showed the following[8-10]:

- a 63% delivery rate after 28 weeks' gestation for physical-exam indicated cerclages in the presence of bulging amniotic membranes
- an 86.2% delivery rate after 32 weeks' gestation for ultrasonography-indicated cerclages
- an 86% delivery rate after 32 weeks' gestation for a history-indicated cerclage in patients with 2 or more prior second-trimester losses.

Success rates, especially for ultrasonography- and history-indicated cerclage, are thus high. For the 14% who still fail these methods, however, a different management strategy is needed, which is where transabdominal cerclage comes into play.

Transabdominal cerclage is an option for certain patients

In transabdominal cerclage, an abdominal approach is used to place a stitch at the cervicouterine junction. With this approach, the cerclage can reach a closer proximity to the internal os compared with the vaginal approach, providing better support of the cervical tissue (**FIGURE 2**).[11] Whether performed via laparotomy or laparoscopy, the transabdominal cerclage procedure likely carries higher morbidity than a transvaginal approach, and cesarean delivery is required after placement.

Since transvaginal cerclage often is successful, in most cases the transabdominal approach should not be viewed as the first-line treatment for cervical insufficiency if a history-indicated transvaginal cerclage has not been attempted. For women who fail a history-indicated transvaginal cerclage, however, a transabdominal cerclage has been proven to decrease the rate of preterm delivery and PPROM compared with attempting another history-indicated transvaginal cerclage.[11,12]

A recent systematic review of pregnancy outcomes after transabdominal cerclage placement reported neonatal survival of 96.5% and an 83% delivery rate after 34 weeks' gestation.[13] Thus, even among a population that failed transvaginal cerclage, a transabdominal cerclage has a high success rate in providing a good pregnancy outcome (**TABLE,** page 40). Transabdominal cerclage also can be considered as first-line treatment in patients who had prior cervical surgery or cervical deformities that might preclude the ability to place a cerclage transvaginally.

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Transabdominal cerclage for managing recurrent pregnancy loss

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TABLE Cerclage indications and success rates[8-10,13]

Type of cerclage	Success rates
History-indicated transvaginal cerclage	86% delivery rate after 32 weeks in patients with 2 or more prior second-trimester losses
Ultrasonography-indicated transvaginal cerclage	86.2% delivery rate after 32 weeks in patients with cervical length < 25 mm
Physical-exam indicated transvaginal cerclage	63% delivery rate after 28 weeks when placed with bulging membranes
Transabdominal cerclage	83% delivery rate after 34 weeks in patients with placement for standard indications

CASE Continued: A candidate for transabdominal cerclage

Given the patient's poor obstetric history, which includes a preterm delivery and neonatal loss despite a history-indicated cerclage, you recommend that the patient have a transabdominal cerclage placed as the procedure has been proven to increase the chances of neonatal survival and delivery after 34 weeks in women with a similar obstetric history. The patient is interested in this option and asks about how this cerclage is placed and when it would need to be placed during her next pregnancy.

FAST TRACK

One study noted that improved obstetric outcomes occurred with interval placement compared with cerclage placement between 9 and 10 weeks' gestation, with a delivery rate at more than 34 weeks in 90% versus 74% of patients, respectively

Surgical technique for transabdominal cerclage placement

A transabdominal cerclage can be placed via laparotomy, laparoscopy, or robot-assisted laparoscopy. No differences in obstetric outcomes have been shown between the laparotomy and laparoscopic approaches.[14,15] Given the benefits of minimally invasive surgery, a laparoscopic or robot-assisted approach is preferred when feasible.

Additionally, for ease of placement, transabdominal cerclage can be placed prior to conception—known as interval placement—or during pregnancy between 10 and 14 weeks (preferably closer to 10 weeks). Because of the increased difficulty in placing a cerclage in the gravid uterus, interval transabdominal cerclage placement is recommended when possible.[13,16] Authors of one observational study noted that improved obstetric outcomes occurred with interval placement compared with cerclage placement between 9 and 10 weeks' gestation, with a delivery rate at more than 34 weeks' gestation in 90% versus 74% of patients, respectively.[16]

Steps for interval cerclage and during pregnancy

Our practice is to place transabdominal cerclage via conventional laparoscopy as an interval procedure when possible. We find no benefit in using robotic assistance.

For an interval procedure, the patient is placed in a dorsal lithotomy position, and we place a 10-mm umbilical port, 2 lateral 5-mm ports, 1 suprapubic 5-mm port, and a uterine manipulator. We use a flexible laparoscope to provide optimal visualization of the pelvis from any angle.

The first step of the surgery involves dissecting the vesicouterine peritoneum in order to move the bladder inferiorly (**FIGURE 3A**). Uterine arteries are then identified lateral to the cervix as part of this dissection, and a window is created in the inferior aspect of the broad ligament just anterior and lateral to the insertion of the uterosacral ligaments onto the uterus, with care taken to avoid the uterine vessels superiorly (**FIGURE 3B**). Two 5-mm Mersilene tape sutures are then tied together to create 1 suture with a needle at each end. This is then passed into the abdomen, and 1 needle is passed through the parametrial space at the level of the internal os inferior to the uterine vessels on 1 side of the uterus while the other needle is passed through the parametrial space on the opposite side.

Alternatively, rather than using the suture needles, a blunt dissector can be passed through this same space bilaterally (**FIGURE 3C**)

via the suprapubic port and can pull the Mersilene tape through the parametrial space (**FIGURE 3D**). The suture is then tied anterior at the level of the internal os intracorporally (**FIGURE 3E**), and the needles are cut off the suture and removed from the abdomen.

To perform transabdominal cerclage when the patient is pregnant, a few modifications are needed to help with placement. First, the patient may be placed in supine position since a uterine manipulator cannot be used. Second, use of a flexible laparoscope becomes even more imperative in order to properly see around the gravid uterus. Lastly, a 5-mm laparoscopic liver retractor can be used to aid in blunt manipulation of the gravid uterus (**FIGURE 3F**). (A surgical video, accompanying this article at mdedge.com/obgyn, highlights the steps to transabdominal cerclage placement in a pregnant patient.) All other port placements and steps to dissection and suture placement are the same as in interval placement.

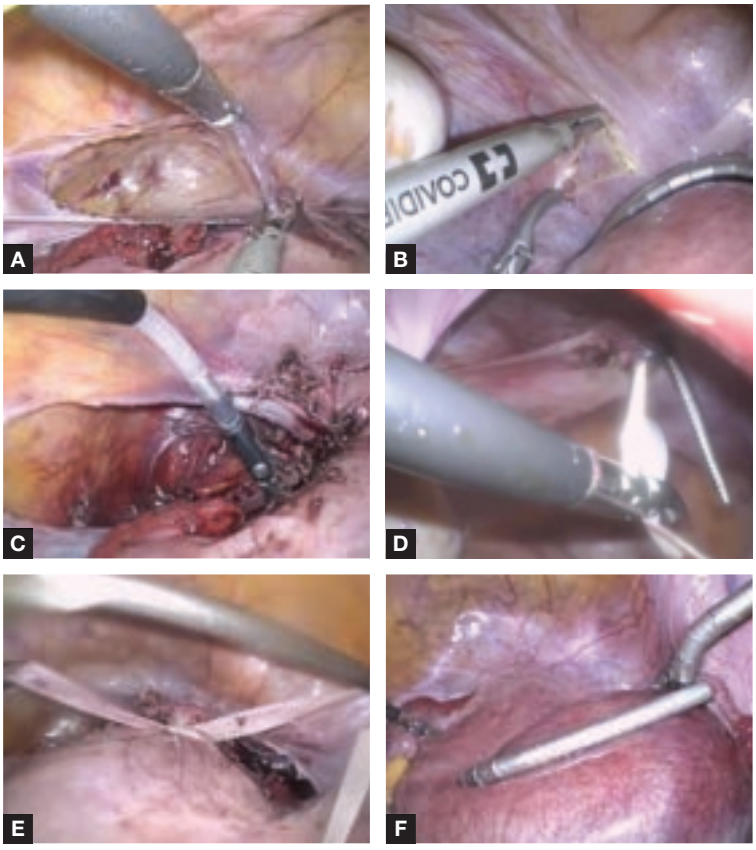
CASE Continued: Patient pursues transabdominal cerclage

You explain to your patient that ideally the cerclage should be placed now in a laparoscopic fashion before she becomes pregnant. You then refer her a local gynecologic surgeon who places many laparoscopic transabdominal cerclages. She undergoes the procedure, becomes pregnant, and after presenting in labor at 35 weeks' gestation has a cesarean delivery. Her baby is born without any neonatal complications, and the patient is overjoyed with the outcome.

Management during and after pregnancy

Pregnant patients with a transabdominal cerclage are precluded from having a vaginal delivery and must deliver via cesarean. During the antepartum period, patients are managed in the same manner as those who have a transvaginal cerclage. Delivery via cesarean at the onset of regular contractions is recommended to reduce the risk of uterine rupture. In the absence of labor, scheduled cesarean is performed at term.

FIGURE 3 Surgical technique for laparoscopic transabdominal cerclage



(**A**) Dissection of the vesicouterine peritoneum. (**B**) Creation of window in broad ligament. (**C**) Passage of blunt dissector through parametrial space. (**D**) Grasping of Mersilene through parametrial space. (**E**) Suture is tied anteriorly. (**F**) Use of liver retractor to manipulate gravid uterus.

Our practice is to schedule cesarean delivery at 38 weeks' gestation, although there are no data or consensus to support a specific gestational age between 37 and 39 weeks. Unlike a transvaginal cerclage, a transabdominal cerclage can be left in place for use in subsequent pregnancies. Data are limited on whether the transabdominal cerclage should be removed in women who no longer desire childbearing and whether there are long-term sequelae if the suture is left in situ.[17]

Complications and risks of abdominal cerclage

As the data suggest and our experience confirms, transabdominal cerclage is highly

successful in patients who have failed a history-indicated transvaginal cerclage; however, the transabdominal approach carries a higher surgical risk. Risks include intraoperative hemorrhage, conversion to laparotomy, and a range of rare surgical and obstetric complications, such as bladder injury and PPROM.[13,18]

If a patient experiences a fetal loss in the first trimester, a dilation and curettage (D&C) can be performed, with good obstetric outcomes in subsequent pregnancies.[19] If the patient experiences an early-to-mid second-trimester loss, some studies suggest that a dilation and evacuation (D&E) of the uterus can be done with sufficient dilation of the cervix to accommodate up to a 15-mm cannula and Sopher forceps.[19] Laminaria also may be used in this process. However, no data exist regarding success of future pregnancies and transabdominal cerclage integrity after a D&E.[20] If the cerclage prevents successful dilation of the cervix, the cerclage must be removed laparoscopically prior to performing the D&E.

In late second-trimester and third-trimester loss, the cerclage must be removed to allow passage of the fetus and placenta prior to a D&E or an induction of labor.[20]

For patients with PPROM or preterm labor, data are limited regarding management recommendations. However, in these complex cases, we strongly recommend an individualized approach and co-management with maternal-fetal medicine specialists.

CASE Resolved

The cerclage is left in place during the patient's cesarean delivery, and her postpartum course is uneventful. She continued without complications for the next year, at which time she sees you in the office with plans to have another pregnancy later in the year. You counsel her that her abdominal cerclage will still be effective and that she can get pregnant with expectations of similar outcomes as her previous pregnancy. She thanks you for everything and reports that she hopes to return later in the year for her first prenatal visit. ●

FAST TRACK

The transabdominal approach carries a higher surgical risk, including intraoperative hemorrhage, conversion to laparotomy, and rare complications such as bladder injury and PPROM

References

1. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 142: Cerclage for the management of cervical insufficiency. *Obstet Gynecol*. 2014;123(2 pt 1):372-379.
2. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev*. 2017;6(6):CD008991.
3. Brown R, Gagnon R, Delisle M-F. No. 373—cervical insufficiency and cervical cerclage. *J Obstet Gynaecol Can*. 2019;41:233-247.
4. Odibo AO, Berghella V, To MS, et al. Shirodkar versus McDonald cerclage for the prevention of preterm birth in women with short cervical length. *Am J Perinatol*. 2007;24:55-60.
5. Basbug A, Bayrak M, Dogan O, et al. McDonald versus modified Shirodkar rescue cerclage in women with prolapsed fetal membranes. *J Matern Fetal Neonatal Med*. 2020;33:1075-1097.
6. Figueroa R, Crowell R, Martinez A, et al. McDonald versus Shirodkar cervical cerclage for the prevention of preterm birth: impact of body mass index. *J Matern Fetal Neonatal Med*. 2019;32:3408-3414.
7. Suhag A, Berghella V. Cervical cerclage. *Clin Obstet Gynecol*. 2014;57:557-567.
8. Bayrak M, Gul A, Goynumer G. Rescue cerclage when foetal membranes prolapse into the vagina. *J Obstet Gynaecol*. 2017;37:471-475.
9. Drassinower D, Coviello E, Landy HJ, et al. Outcomes after periviable ultrasound-indicated cerclage. *J Matern Fetal Neonatal Med*. 2019;32:932-938.
10. Lee KN, Whang EJ, Chang KH, et al. History-indicated cerclage: the association between previous preterm history and cerclage outcome. *Obstet Gynecol Sci*. 2018;61:23-29. doi:10.5468/ogs.2018.61.1.23.
11. Sneider K, Christiansen OB, Sundtoft IB, et al. Recurrence rates after abdominal and vaginal cerclages in women with cervical insufficiency: a validated cohort study. *Arch Gynecol Obstet*. 2017;295:859-866.
12. Davis G, Berghella V, Talucci M, et al. Patients with a prior failed transvaginal cerclage: a comparison of obstetric outcomes with either transabdominal or transvaginal cerclage. *Am J Obstet Gynecol*. 2000;183:836-839.
13. Moawad GN, Tyan P, Bracke T, et al. Systematic review of transabdominal cerclage placed via laparoscopy for the prevention of preterm birth. *J Mimim Invasive Gynecol*. 2018;25:277-286.
14. Burger NB, Brölmann HAM, Einarsson JI, et al. Effectiveness of abdominal cerclage placed via laparotomy or laparoscopy: systematic review. *J Minim Invasive Gynecol*. 2011;18:696-704.
15. Kim S, Hill A, Menderes G, et al. Minimally invasive abdominal cerclage compared to laparotomy: a comparison of surgical and obstetric outcomes. *J Robot Surg*. 2018;12:295-301.
16. Dawood F, Farquharson RG. Transabdominal cerclage: preconceptual versus first trimester insertion. *Eur J Obstet Gynecol Reprod Biol*. 2016;199:27-31.
17. Hawkins E, Nimaroff M. Vaginal erosion of an abdominal cerclage 7 years after laparoscopic placement. *Obstet Gynecol*. 2014;123(2 pt 2 suppl 2):420-423.
18. Foster TL, Moore ES, Sumners JE. Operative complications and fetal morbidity encountered in 300 prophylactic transabdominal cervical cerclage procedures by one obstetric surgeon. *J Obstet Gynaecol*. 2011;31:713-717.
19. Dethier D, Lassey SC, Pilliod R, et al. Uterine evacuation in the setting of transabdominal cerclage. *Contraception*. 2020;101:174-177.
20. Martin A, Lathrop E. Controversies in family planning: management of second-trimester losses in the setting of an abdominal cerclage. *Contraception*. 2013;87:728-731.

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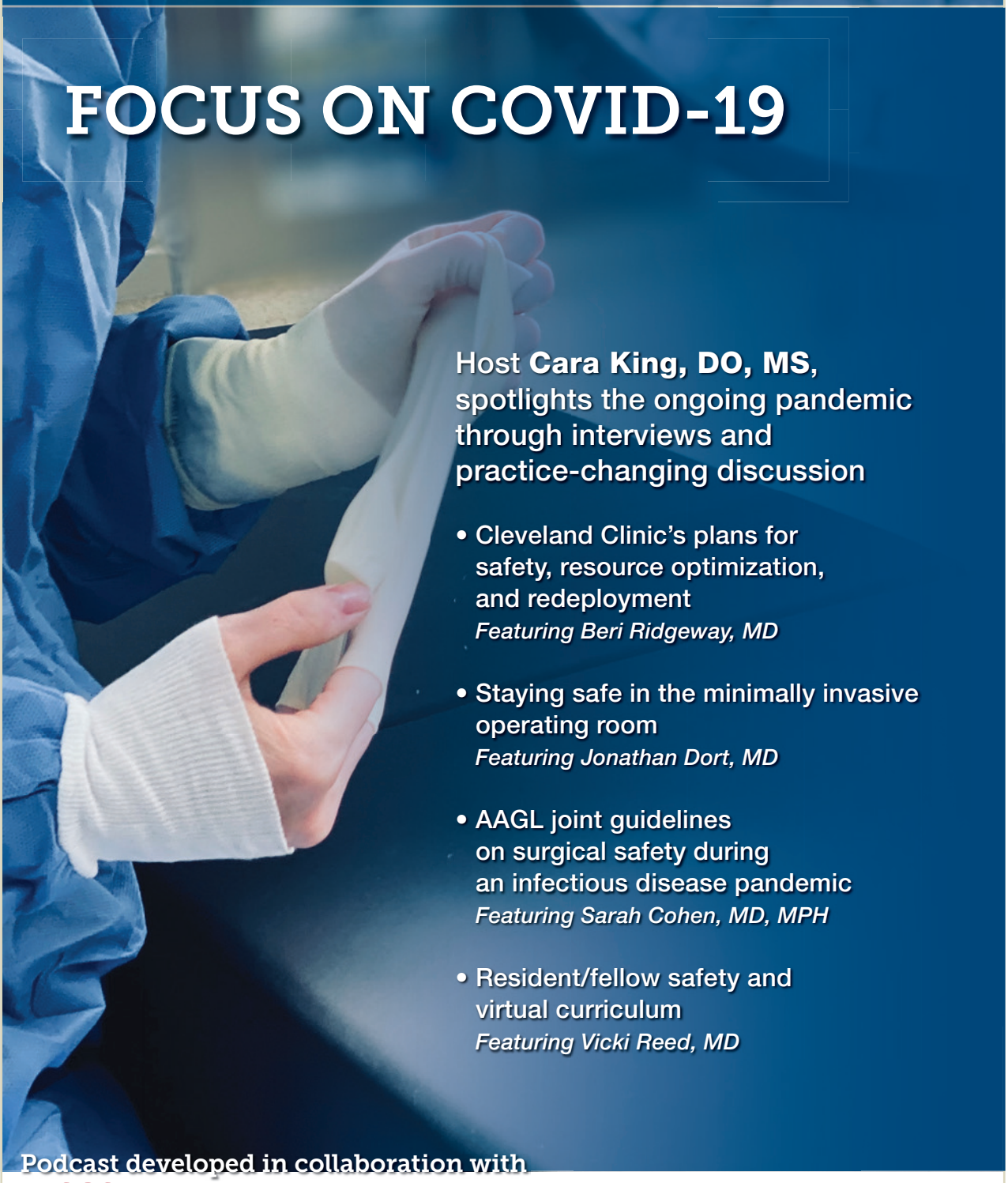

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COVID-19 apps for the ObGyn health care provider

Three apps to help clinicians keep up with COVID-19 information and treatment guidance

Kelly Bogaert, MD, and Katherine T. Chen, MD, MPH

IN THIS ARTICLE

Details on recommended apps
page 46

In the midst of the coronavirus disease 2019 (COVID-19) pandemic, health care providers, including ObGyns, need up-to-date information to keep pace with the ever-changing health care crisis. Literature regarding obstetric populations is emerging in journals.[1,2] General guidance in the management of COVID-19–positive patients may also be helpful to the ObGyn provider. Although scientific journals are now publishing COVID-19 research at warp speed, those same journals tend to be too specialized for general readers.[3] Mobile apps may make the information more accessible.

This app review focuses on 3 apps that provide information about the ongoing COVID-19 pandemic and detail general guidance for treatment of COVID-19–positive patients. An initial search in early April 2020 of major national health care organizations and ObGyn-specific organizational apps yielded the Centers for Disease Control and Prevention (CDC) app. A subsequent search in the app stores using the term "COVID" yielded 2 additional apps: the Osler COVID Learning Centre app and the Relief Central app.

The CDC app contains a COVID-19-specific section that highlights pertinent information for health care providers as well as a section on caring for the obstetric patient. The Osler app includes podcasts and

CONTINUED ON PAGE 46

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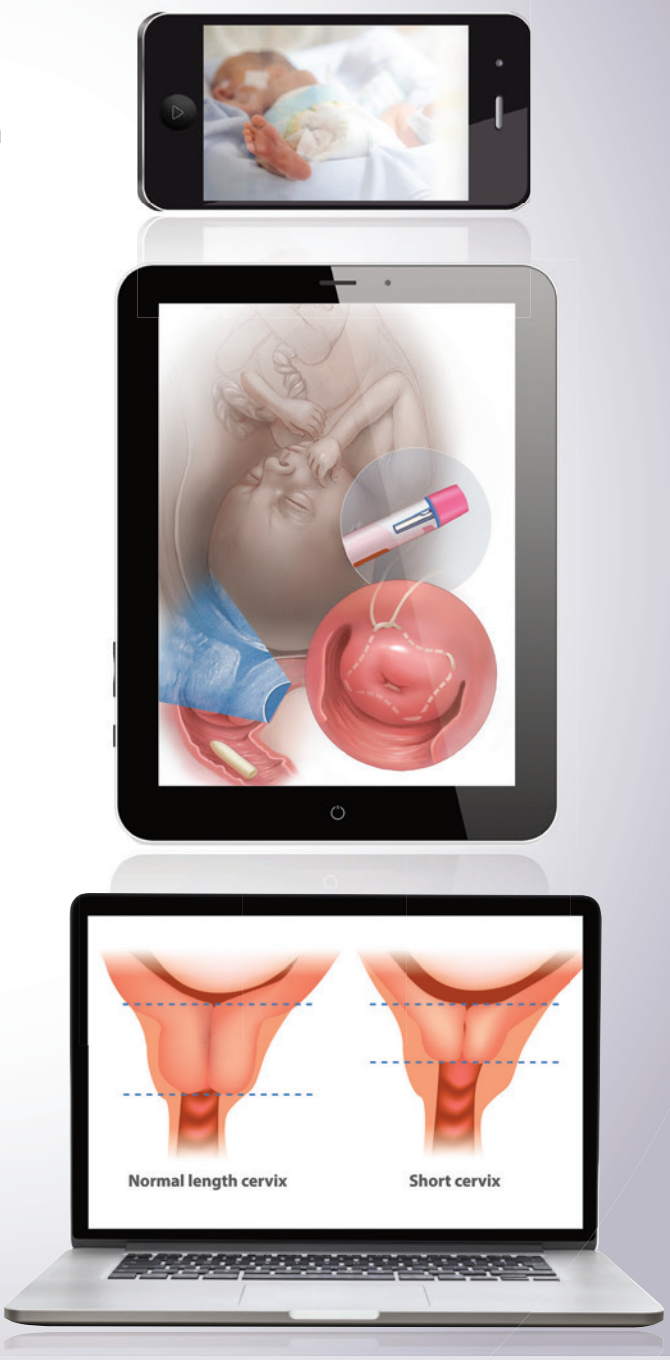

OBG MANAGEMENT

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CONTINUED FROM PAGE 44

TABLE Recommended COVID-19 apps

App	App comprehensiveness	Price	Platform	Literature used	Important special features
CDC iTunes: https://apps.apple.com/us/app/cdc/id487847188 Google Play: https://play.google.com/store/apps/details?id=gov.cdc.general&hl=en_US	• Clinical decision making (clinical treatment guidelines) • Reference and information (medical news)	Free	iTunes and Google Play store	CDC website	• Daily updates • Links to CDC updates and policies • Section on care for pregnant patients • Guidelines for workplace exposure, infection control, and PPE
Osler COVID Learning Centre iTunes: https://apps.apple.com/au/app/osler-covid-learning-centre/id1504015523	• Clinical decision making (clinical treatment guidelines) • Reference and information (medical news)	Free	iTunes	External links to health care organization websites (eg, WHO, academic institutions)	• Weekly updates • Podcasts on COVID-19 • Skills videos related to critical care • Extensive list of links related to COVID-19
Relief Central iTunes: https://apps.apple.com/us/app/relief-central/id353219185	• Clinical decision making (clinical treatment guidelines) • Reference and information (medical news)	Free	iTunes	CDC, WHO, PubMed, and journal links	• Weekly updates • Current treatment updates with literature citations • Guidance on specimen collections

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; PPE, personal protective equipment; WHO, World Health Organization.

videos on critical care for noncritical care providers. Finally, the Relief Central app contains updated information on screening and treatment for COVID-19. The **TABLE** features details of the 3 apps.

Each app is evaluated based on a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature use, and important special features).[4]

References

1. Rasmussen SA, Smulian JC, Lednicky JA, et al. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol.* February 24, 2020. doi:10.1016/j.ajog.2020.02.017.
2. Dashraath P, Jing Lin Jeslyn W, Mei Xian Karen L, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol.* March 23, 2020. doi:10.1016/j.ajog.2020.03.021.
3. Tingley K. Coronavirus is forcing medical research to speed up. *New York Times Magazine.* April 26, 2020:16-18.
4. Chyjek K, Farag S, Chen KT. Rating pregnancy wheel applications using the APPLICATIONS scoring system. *Obstet Gynecol.* 2015;125:1478-1483.

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Do women treated with ceftriaxone and doxycycline for PID benefit from added metronidazole to broaden anaerobic coverage?

Yes, results from a randomized trial noted a therapeutic benefit in women with pelvic inflammatory disease (PID) who were treated with the addition of metronidazole as they were less likely to have pelvic organ tenderness a month after enrollment than those who received placebo (9% vs 20%, respectively). Their concurrent disorders of bacterial vaginosis and trichomonas vaginitis were more effectively treated, and they had fewer follow-up endometrial cultures that were positive for anaerobic bacteria than the placebo group (8% vs 21%, respectively). Moreover, the combination regimen was no more likely to cause gastrointestinal adverse effects than doxycycline alone.

FAST TRACK

While anaerobes are more commonly isolated from the upper genital tract of patients with acute PID than N gonorrhoeae *or* C trachomatis, *recommended treatments do not necessarily include antibiotics with an antianaerobic spectrum*

Wiesenfeld HC, Meyn LA, Darville T, et al. A randomized controlled trial of ceftriaxone and doxycycline, with or without metronidazole, for the treatment of acute pelvic inflammatory disease. Clin Infect Dis. February 13, 2020. doi:10.1093/cid/ciaa101.

EXPERT COMMENTARY
David E. Soper, MD, is Paul B. Underwood III Professor, Vice Chairman, Department of Obstetrics and Gynecology, Senior Medical Director, Women's Health, Medical University of South Carolina, Charleston.

Pelvic inflammatory disease remains prevalent among young women and is commonly diagnosed in emergency departments and sexually transmitted disease (STD) clinics. This tubal infection is associated with significant reproductive sequelae, including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. In addition, these women remain at risk for recurrent PID.

Bacterial vaginosis is present in more than half of women with PID. Not surprisingly, anaerobic microorganisms are more commonly isolated from the upper genital tract of patients with acute PID than either *Neisseria gonorrhoeae* or *Chlamydia trachomatis,* yet recommended antimicrobial regimens do not necessarily include antibiotics with an excellent antianaerobic spectrum.

The author reports no financial relationships relevant to this article.

Details of the study

In a randomized, double-blind, placebo-controlled trial, Wiesenfeld and colleagues enrolled women from hospital emergency departments or an STD clinic with symptoms

of lower abdominal or pelvic pain associated with pelvic organ tenderness. The 233 study participants were randomly assigned to 2 treatment arms: ceftriaxone, doxycycline, and placebo (n = 117) or ceftriaxone, doxycycline, and metronidazole (n = 116).

Findings. Women treated with metronidazole were less likely to have pelvic organ tenderness a month after enrollment compared with the placebo group (9% vs 20%, respectively). Although the clinical cure rates at 30 days were statistically similar in both arms of the study, those receiving metronidazole had a 97% clinical cure rate while those not treated with metronidazole had a 90% clinical cure rate ($P = .38$).

Moreover, the concurrent disorders of bacterial vaginosis and trichomonas vaginitis were more effectively treated in the metronidazole group, and fewer women had positive follow-up endometrial cultures for anaerobic bacteria compared with the placebo group (8% vs 21%, respectively).

The anticipated gastrointestinal adverse effects of a combination doxycycline-and-metronidazole regimen was a significant concern; however, combination therapy was no more likely to cause gastrointestinal adverse effects than doxycycline alone.

Study strengths and limitations

This well-designed randomized, double-blinded clinical trial was performed by clinical investigators experienced in the clinical diagnosis of PID. The demography of the population and their history of *C trachomatis, N gonorrhoeae,* plus the concurrent diagnosis of bacterial vaginosis make the diagnosis believable and real world, and these factors contribute to the generalizability of the study results.

However, PID is an imprecise clinical diagnosis (specificity averages 65%) when held to the gold standard of diagnostic laparoscopy to confirm the presence of acute salpingitis. Given the reticence of investigators and clinicians to embark on such an invasive procedure to confirm this diagnosis, endometrial biopsy showing evidence of histologic acute endometritis has been offered as an alternative gold standard. Confirmation of acute endometritis in the trial participants would have enhanced the validity of this study.

This study challenges a long held, but never proven, belief that the combination of doxycycline and metronidazole would be poorly tolerated as a combination antimicrobial regimen. It also further solidifies the role of anaerobic bacteria as major players in the microbial etiology of acute PID. In addition, it appears that treating bacterial vaginosis concurrently may lessen the likelihood of endometrial recolonization with anaerobic bacteria. ●

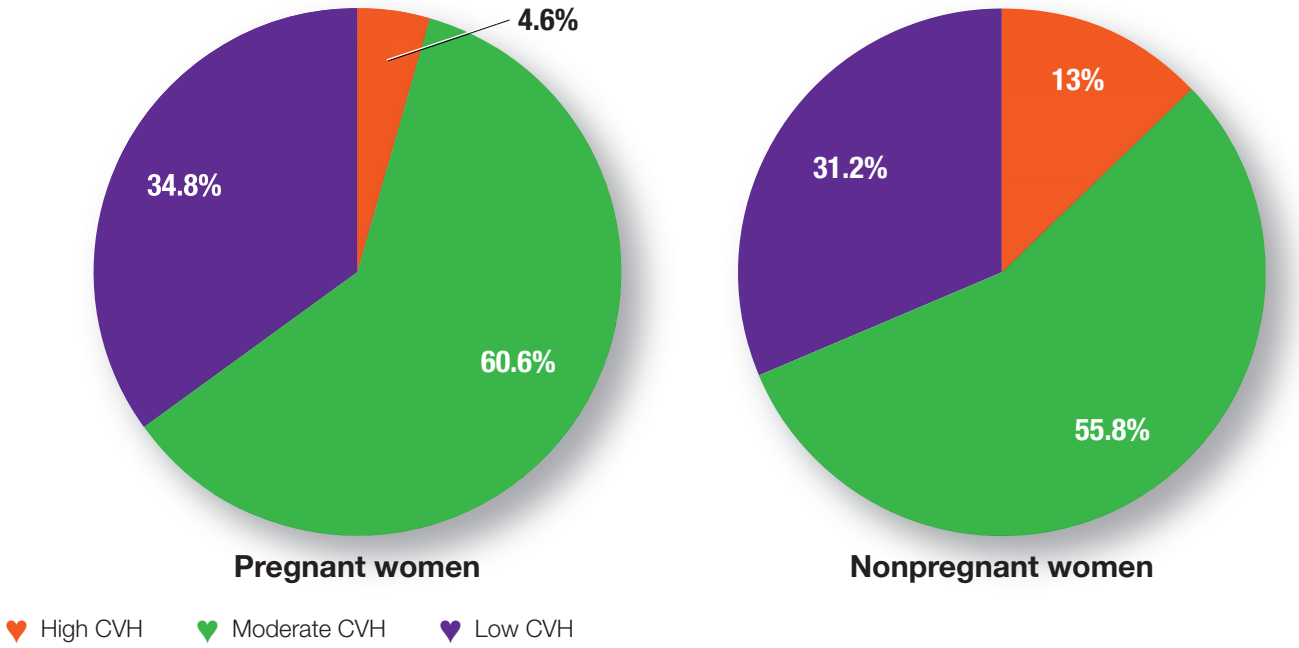
WHAT THIS EVIDENCE MEANS FOR PRACTICE

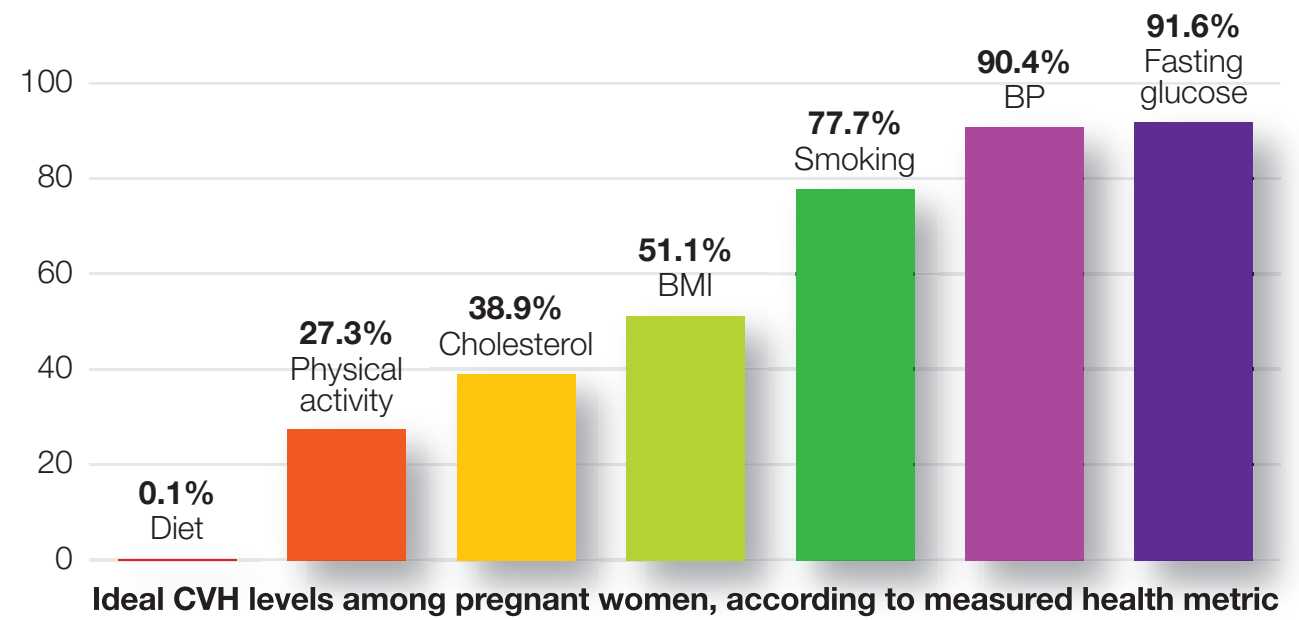
Metronidazole should be added routinely to the standard antibiotic regimen of ceftriaxone and doxycycline for the treatment of women with PID.

DAVID E. SOPER, MD

Cardiovascular health among US pregnant women

The American Heart Association and the American College of Obstetricians and Gynecologists have described pregnancy as a "physiological 'stress test' that reveals underlying risk for cardiovascular disease," and they promote women's cardiovascular health (CVH) across the lifespan. CVH has been shown to predict positive health outcomes in nonpregnant adults. To assess overall CVH[a] among US pregnant women aged 20 to 44 years from 1999 to 2014, researchers measured 7 CVH metrics, comparing overall CVH with that among nonpregnant women.





Ideal CVH levels among pregnant women, according to measured health metric

[a]Total CVH scores calculated by assigning 2 points for each ideal metric, 1 point for intermediate, and 0 points for poor or nonideal. Points were summed across the 7 metrics to calculate total CVH scores, classified as 12 to 14 high, 8 to 11 moderate, and 0 to 7 low.

Source: Perak AM, Ning H, Khan SS, et al. Cardiovascular health among pregnant women, aged 20 to 44 years, in the United States. *J Am Heart Assoc*. 2020;9:e015123. DOI:10.1161/JAHA.119.015123.

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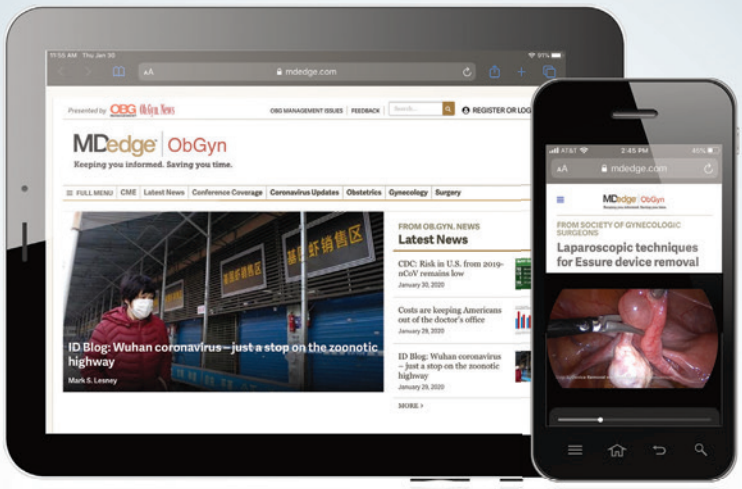

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