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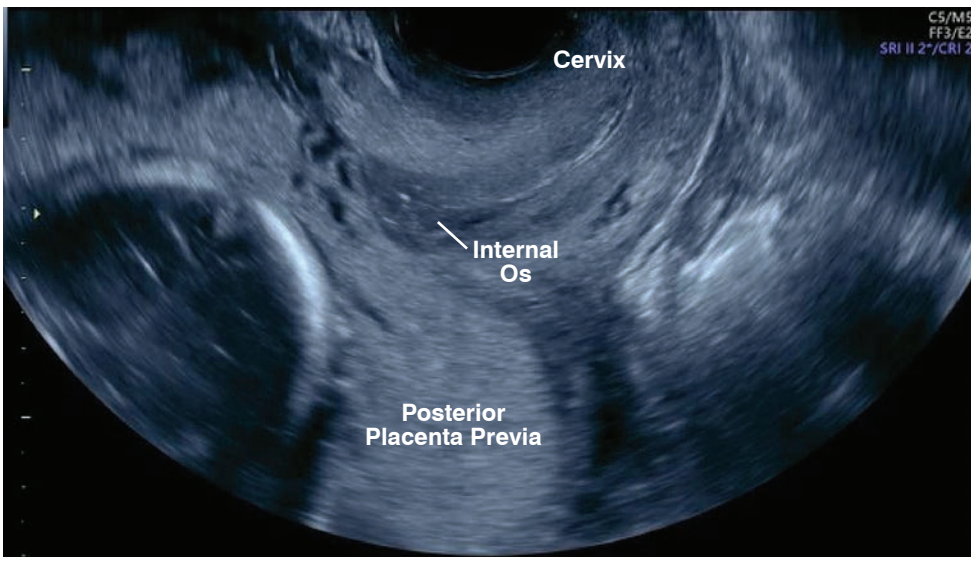



OBSTETRICS

# Placenta previa

## Utilizing sonograms for evaluation and management

By Reem S. Abu-Rustum, MD, FACOG, FACS, FAIUM



ContemporaryOBGYN.net


*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 (due to risk of bone loss), 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.

abbvie 

## WITH DOSE-DEPENDENT EFFICACY, CHOOSE THE DOSAGE BASED ON HER NEEDS[1]

**The dose-dependent efficacy and safety results of ORILISSA help you choose the most appropriate dosage for your patients based on symptom severity and treatment objectives.[1]**

**Proven relief of moderate to severe pain associated with endometriosis**

Dysmenorrhea
Non-menstrual Pelvic Pain

**150 mg QD**

Dysmenorrhea
Non-menstrual Pelvic Pain
Dyspareunia

**200 mg BID**

Tablets and packages pictured are not actual size.

### 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.

**Consider the proven efficacy of ORILISSA as a next step for her.[1]**
**Explore more at ORILISSA.com/hcp**

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.

**Reference: 1.** Orilissa [package insert]. North Chicago, IL: AbbVie Inc; 2018.

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

Orilissa®
elagolix tablets 150mg 200mg

# 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 because of the risk of bone loss *[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**

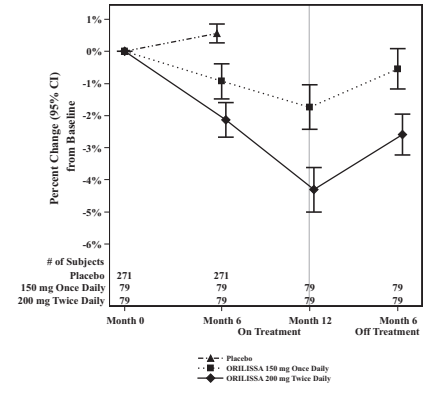
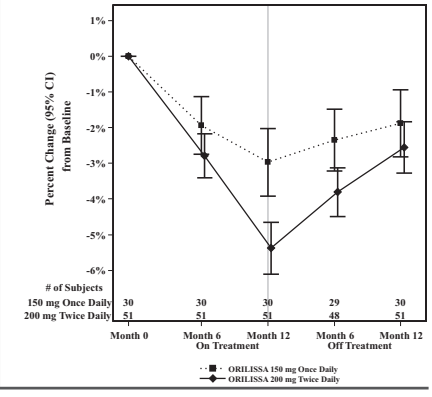



**Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4**



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 | |
|---|---|---|---|---|---|---|
| | Baseline | Month 3 | Baseline | Month 3 | Baseline | 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 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. |
| Antimycobacteria 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. |

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

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]*.
- 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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# CHAIRMAN'S LETTER

# Placenta previa, UTx, and more this month

For more than 45 years, it has been our privilege at *Contemporary OB/GYN* to bring you the best in evidence-based practice and scientific advancements in a clinically useful format. We want to be your go-to source of practical, authoritative information on the latest advances in women's health - and each issue is crafted with that goal in mind.

This month, we're featuring an article about sonographic examination in the diagnosis of placenta previa, one of the complications linked to previous uterine surgeries, including past cesarean sections. Because cesarean sections account for 32% of all births in the United States, determining the placenta's location as early as possible allows for the identification of pregnancies at risk for complications such as bleeding and accreta. In this piece, Dr. Reem Abu-Rustum of the University of Florida College of Medicine, Gainesville, discusses what practitioners need to know.

More and more, news stories are reporting a live birth to a mother who received a uterine transplant (UTx). This ground-breaking surgery is a boon to women who suffer from absolute uterine factor infertility (AUFI), giving them the opportunity to become pregnant when, just a generation ago, the possibility didn't exist. The uterine transplant program at Cleveland Clinic is distinct in that it only uses uteri from deceased donors for its transplant surgeries. Earlier this summer, one of these transplants resulted in a successful live birth. This month, two members of the Cleveland Clinic team discuss the uterine transplant surgery as it is performed in that facility and its implications for patients with AUFI.

In addition, we look at the challenge of caring for patients with endometriosis. As much as any other, this disease demands that patient and physician work as a team, perhaps over an extended period of time, to determine the extent of the disease and the best course of treatment. Dr. Mobolaji Ajao of Harvard, who previously wrote a compelling cover story on 3D modeling in gyn surgery, now turns his attention to what all generalists need to know about endometriosis, diagnosis and treatment.

While you're immersed in our pages, don't miss reading our popular Legally Speaking column, which is a favorite among our readers based on our latest market research. This month, we examine the question of which practitioner is ultimately responsible for the care of high-risk patients.

We hope you enjoy this month's issue. For even more great content, visit us online at Contemporary obgyn.net.

We take our mission – to help you improve your practice – very seriously. For that reason, we encourage you to contact us at COGEditorial@mmhgroup.com and let us how we're doing. ■

Mike Hennessy, Sr.
**Chairman and Founder**
**MJH Life Sciences**

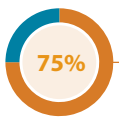
Enhancing patient outcomes, managing costs, and optimizing quality of life.

# The value of care:

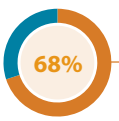
## UNIVERSAL SCREENING
for Chlamydia and Gonorrhea

About **ONE** in **TWO** sexually active people will acquire an STI by **AGE 25.**

Infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are commonly asymptomatic.




~75% of women infected with **chlamydia** are asymptomatic[1]




~68% of women infected with **gonorrhea** are asymptomatic[1]

Chlamydia and gonorrhea are two of the most common reportable sexually transmitted infections (STIs) and rates of infection are on the rise.

**A universal screening CT/NG strategy** would focus on women within the high-risk age group covered by guidelines from USPSTF and CDC guidelines (women 15-24 years old) without regard to the sexual activity they report.

**Universal screening may help to:**[2]

- Decrease STI prevalence
- Decrease infertility due to undiagnosed infections
- Reduce health care cost

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2. Owusu-Edusei K, Hoover KW, Gift TL. Cost-effectiveness of opt-out chlamydia testing for high-risk young women in the U.S. *Am J Prev Med.* 2016;51(2):216-24. doi: 10.1016/j.amepre.2016.01.007.

# IN THIS ISSUE

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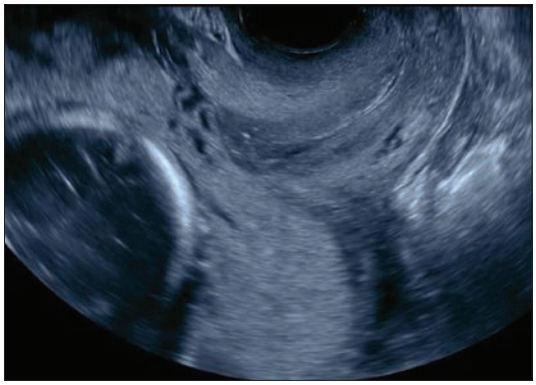



**CORRECTION** In the article "Alternatives to traditional surgery for fibroids" which appeared in the September 2019 issue it was noted that neither author had any disclosures. Dr. Elizabeth Stewart, lead author, receives a royalty from UpToDate, consulting fees from Bayer and Myovant, and provides CME preparation for Peer View. The editors apologize for these omissions.

COVER IMAGE: PROVIDED BY AUTHOR

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Multimodal pain management with **EXPAREL** provided significantly better pain control after C-section vs multimodal protocols alone[1,2] and...

**52%** **REDUCED postsurgical opioid use*** (MED) over 72 hours vs standard bupivacaine TAP block ($P$=0.0117)[2†]

**12 hours** **REDUCED time to ambulation** vs multimodal protocol without EXPAREL ($P$<0.001)[1‡]

**1 day** **REDUCED hospital LOS** by 1 day ($P$<0.001); 2.9 days (n=97) vs 3.9 days (n=89)[1‡]

Improve clinical and economic outcomes. **Learn more at www.EXPAREL.com/OBGyn**

LOS, length of stay; MED, morphine equivalent dose; TAP, transversus abdominis plane.
*The clinical benefit of the decrease in opioid consumption was not demonstrated in the pivotal trials.
†A prospective, 13-site, multicenter, randomized clinical trial of 186 patients who underwent a C-section with a multimodal pain management protocol, including a TAP block using either 20 mL EXPAREL 266 mg, 20 mL 0.25% bupivacaine HCl, and 20 mL normal saline (30 mL volume on each side) for a total volume of 60 mL; or 20 mL 0.25% bupivacaine HCl and 40 mL normal saline (30 mL volume on each side) for a total volume of 60 mL.[2,3]
‡Single-center retrospective trial of 201 patients who underwent C-section with either a multimodal pain management protocol including a TAP block with 20 mL EXPAREL 266 mg, 30 mL 0.25% bupivacaine HCl, and 30 mL normal saline; or a multimodal pain management protocol alone. Mean hospital LOS was 2.9 days with EXPAREL (n=97) vs 3.9 days without EXPAREL (n=89). Time to ambulation was 18.7 hours with EXPAREL (n=67) and 30.7 hours without EXPAREL (n=60).[1]

**Indication**
EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

**Important Safety Information**
EXPAREL is contraindicated in obstetrical paracervical block anesthesia. Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation. If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine. EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.
**Warnings and Precautions Specific to EXPAREL:** Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL. EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks **other than interscalene brachial plexus nerve block**, or intravascular or intra-articular use. The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.
**Warnings and Precautions for Bupivacaine-Containing Products**
**Central Nervous System (CNS) Reactions:** There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression. **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death. **Allergic Reactions:** Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use. **Methemoglobinemia:** Cases of methemoglobinemia have been reported with local anesthetic use.

**Please refer to brief summary of full Prescribing Information on adjacent page.**
**Full Prescribing Information is available at www.EXPAREL.com.**
**For more information, please visit www.EXPAREL.com or call 1-855-RX-EXPAREL (793-9727).**

**References: 1.** Baker BW, Villadiego LG, Lake YN, et al. Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. *J Pain Res.* 2018;11:3109-3116. **2.** Habib AS, Nedeljkovic SS, Kett A, et al. Liposomal bupivacaine transversus abdominis plane block for pain after cesarean delivery: results from a multicenter, randomized, double-blind, controlled trial. Presented at: SOAP 51st Annual Meeting; May 4, 2019; Phoenix, AZ. **3.** ClinicalTrials.gov website. Evaluate the safety and efficacy of EXPAREL when administered via infiltration into the TAP vs bupivacaine alone in subjects undergoing elective c-sections (c-section). https://clinicaltrials.gov/ct2/show/NCT03176459. Updated April 22, 2019. Accessed May 31, 2019.

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Parsippany, NJ 07054 PP-EX-US-4978 07/19

# EXPAREL®

(bupivacaine liposome injectable suspension)

**Brief Summary**
**(For full prescribing information refer to package insert)**

## INDICATIONS AND USAGE

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

Limitation of Use: Safety and efficacy has not been established in other nerve blocks.

## CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

## WARNINGS AND PRECAUTIONS

**Warnings and Precautions Specific for EXPAREL**

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks other than interscalene brachial plexus nerve block
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups.

- patients younger than 18 years old
- pregnant patients

The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days as seen in clinical trials.

## ADVERSE REACTIONS

**Clinical Trial Experience**

Adverse Reactions Reported in Local Infiltration Clinical Studies

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting. The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

Adverse Reactions Reported in Nerve Block Clinical Studies

The safety of EXPAREL was evaluated in four randomized, double-blind, placebo-controlled nerve block clinical studies involving 469 patients undergoing various surgical procedures. Patients were administered a dose of either 133 or 266 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, pyrexia, and constipation.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration as a nerve block were muscle twitching, dysgeusia, urinary retention, fatigue, headache, confusional state, hypotension, hypertension, hypoesthesia oral, pruritus generalized, hyperhidrosis, tachycardia, sinus tachycardia, anxiety, fall, body temperature increased, edema peripheral, sensory loss, hepatic enzyme increased, hiccups, hypoxia, post-procedural hematoma.

Postmarketing Experience

These adverse reactions are consistent with those observed in clinical studies and most commonly involve the following system organ classes (SOCs): Injury, Poisoning, and Procedural Complications (e.g., drug-drug interaction, procedural pain), Nervous System Disorders (e.g., palsy, seizure), General Disorders And Administration Site Conditions (e.g., lack of efficacy, pain), Skin and Subcutaneous Tissue Disorders (e.g., erythema, rash), and Cardiac Disorders (e.g., bradycardia, cardiac arrest).

## DRUG INTERACTIONS

The toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity. Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

Patients who are administered local anesthetics may be at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

**Examples of Drugs Associated with Methemoglobinemia:**

| Class | Examples |
|---|---|
| Nitrates/Nitrites | nitric oxide, nitroglycerin, nitroprusside, nitrous oxide |
| Local anesthetics | articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine |
| Antineoplastic agents | cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase |
| Antibiotics | dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides |
| Antimalarials | chloroquine, primaquine |
| Anticonvulsants | Phenobarbital, phenytoin, sodium valproate |
| Other drugs | acetaminophen, metoclopramide, quinine, sulfasalazine |

Bupivacaine

Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

Non-bupivacaine Local Anesthetics

EXPAREL should not be admixed with local anesthetics other than bupivacaine. Nonbupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. There are no data to support administration of other local anesthetics prior to administration of EXPAREL.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

Water and Hypotonic Agents

Do not dilute EXPAREL with water or other hypotonic agents, as it will result in disruption of the liposomal particles

## USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary

There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose equivalent to 1.6 times the maximum recommended human dose (MRHD) of 266 mg. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.5 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risks to a fetus.

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

Clinical Considerations

Labor or Delivery

Bupivacaine is contraindicated for obstetrical paracervical block anesthesia. While EXPAREL has not been studied with this technique, the use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death.

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Data

Animal Data

Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard plate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) and rabbit doses were 1.3, 5.8, and 22.2 mg/kg/day (equivalent to 0.1, 0.4 and 1.6 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Decreased pup survival was noted at 1.5 times the MRHD in a rat pre- and post-natal development study when pregnant animals were administered subcutaneous doses of 4.4, 13.3, and 40 mg/kg/day buprenorphine hydrochloride (equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight) from implantation through weaning (during pregnancy and lactation).

**Lactation**

Risk Summary

Limited published literature reports that bupivacaine and its metabolite, pipecoloxylidide, are present in human milk at low levels. There is no available information on effects of the drug in the breastfed infant or effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXPAREL and any potential adverse effects on the breastfed infant from EXPAREL or from the underlying maternal condition.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the total number of patients in the EXPAREL local infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. Of the total number of patients in the EXPAREL nerve block clinical studies (N=531), 241 patients were greater than or equal to 65 years of age and 60 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Hepatic Impairment**

Amide-type local anesthetics, such as bupivacaine, are metabolized by the liver. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations, and potentially local anesthetic systemic toxicity. Therefore, consider increased monitoring for local anesthetic systemic toxicity in subjects with moderate to severe hepatic disease.

**Renal Impairment**

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. This should be considered when performing dose selection of EXPAREL.

## OVERDOSAGE

Clinical Presentation

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution.

Signs and symptoms of overdose include CNS symptoms (perioral paresthesia, dizziness, dysarthria, confusion, mental obtundation, sensory and visual disturbances and eventually convulsions) and cardiovascular effects (that range from hypertension and tachycardia to myocardial depression, hypotension, bradycardia and asystole).

Plasma levels of bupivacaine associated with toxicity can vary. Although concentrations of 2,500 to 4,000 ng/mL have been reported to elicit early subjective CNS symptoms of bupivacaine toxicity, symptoms of toxicity have been reported at levels as low as 800 ng/mL.

Management of Local Anesthetic Overdose

At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to the use of anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine to enhance myocardial contractile force).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, maybe indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

## DOSAGE AND ADMINISTRATION

**Important Dosage and Administration Information**

- EXPAREL is intended for single-dose administration only.
- Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL.
- DO NOT dilute EXPAREL with water for injection or other hypotonic agents, as it will result in disruption of the liposomal particles.
- Use suspensions of EXPAREL diluted with preservative-free normal (0.9%) saline for injection or lactated Ringer's solution within 4 hours of preparation in a syringe.
- Do not administer EXPAREL if it is suspected that the vial has been frozen or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- Inspect EXPAREL visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer EXPAREL if the product is discolored.

**Recommended Dosing in Adults**

Local Analgesia via Infiltration

The recommended dose of EXPAREL for local infiltration in adults is up to a maximum dose of 266mg (20 mL), and is based on the following factors:

- Size of the surgical site
- Volume required to cover the area
- Individual patient factors that may impact the safety of an amide local anesthetic

As general guidance in selecting the proper dosing, two examples of infiltration dosing are provided:

- In patients undergoing bunionectomy, a total of 106 mg (8 mL) of EXPAREL was administered with 7 mL infiltrated into the tissues surrounding the osteotomy, and 1 mL infiltrated into the subcutaneous tissue.
- In patients undergoing hemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

Regional Analgesia via Interscalene Brachial Plexus Nerve Block

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL), and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair.

**Compatibility Considerations**

Admixing EXPAREL with drugs other than bupivacaine HCl prior to administration is not recommended.

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2.

  The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

**Non-Interchangeability with Other Formulations of Bupivacaine**

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

## CLINICAL PHARMACOLOGY

**Pharmacokinetics**

Administration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after interscalene brachial plexus nerve block. In general, peripheral nerve blocks have shown systemic plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

## PATIENT COUNSELING

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

PACIRA PHARMACEUTICALS, INC.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

6,132,766 5,891,467 5,766,627 8,182,835



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**Rx only** **November 2018**

# EDITORIAL

*by* HAYWOOD L. BROWN, MD, AND ALEXANDRA ANDES

# Reproductive health care in America: A story of give and take

Fifty years after Roe and Title X, the right to reproductive freedom continues to come under fire.

Women's reproductive freedom has advanced significantly over the past 100 years. Abortion rates have steadily declined in the United States over the last quarter century, falling to 14.6 abortions per 1,000 women aged 15 to 44 in 2014, the lowest rate ever recorded.[1] As pointed out by the authors of this report, the overwhelming majority of abortions occur in the first trimester. Second-trimester abortions account for only a small fraction of all abortions in the United States; as of 2015, 7.6% of all abortions occurred between 14 and 20 weeks and only 1.4% occurred at 21 weeks or more. However, as abortion rates fall the obstacles to access for first-trimester and more critically second-trimester procedures have become increasingly burdensome.

## Historical perspective on abortion

Before 1880, abortion was commonly practiced in the United States. Over the next half century, anti-abortion sentiments began to increase in response to the growing movements for women's suffrage and birth control. Many states passed legislation that confined women to traditional childbearing roles and banned abortion except in extreme circumstances. These regulations forced women to seek illegal abortions from unregulated, often unskilled abortion providers or to use unsafe self-induced methods which often led to sepsis and, sometimes, death.

The Comstock Act of 1873, an "Act of the Suppression of Trade in, and Circulation of, Obscene Literature and Articles of Immoral Use," criminalized publication, distribution, and possession of information about devices or medications for "unlawful" abortion or contraception.[2] Violators faced a fine and imprisonment. Although vestiges of the act remained into the 1990s, Congress removed most of the contraception-related language in 1971.

In the late 1960s, the Clergy Consultation Service on Abortion, a network of concerned pastors and rabbis, set up referral services to help women find safer procedures. Between 1967 and 1973, 14 states reformed their abortion statutes in favor of women seeking safer abortion care; four states repealed restrictive abortion laws.

In the landmark *Roe v Wade* (1973), the U.S. Supreme Court ruled that the Constitution of the United States protects a pregnant woman's liberty to choose to have an abortion without excessive government restriction.[3] Following that decision, which established this "right to privacy" as related to abortion care, federal- and state-funded Medicaid programs covered abortion as part of comprehensive healthcare services for low-income women. The Roe Supreme Court decision (410 US 113) ruled on the constitutionality of laws that criminalized or restricted access to abortions. Before Roe legalized abortion, dedicated, well-trained physicians and other medical practitioners risked imprisonment, fines, and loss of their medical licenses to provide abortions. Then came the Hyde Amendment, passed by Congress in 1976 and renewed every year since, that bans use of federal funding for abortion care except in limited cases. Because so many women depend upon Medicaid for their health care, the Hyde Amendment effectively makes it much more difficult for women of lower socioeconomic status—disproportionately women of color— and adolescent girls who are also disproportionately represented in rates of unintended pregnancy and subsequent abortion to get abortion care. Today, several states have initiated legislation (heartbeat bills) that would again go as far as to criminalize performing an abortion, and the Hyde Amendment still lives.

CONTINUED ON PAGE 42

# Practical approach to sonographic evaluation and management of Placenta previa

Identifying abnormal placentation is crucial for determining the correct management of at-risk pregnancies and minimizing morbidity and mortality of both mother and child.

*by* REEM S. ABU-RUSTUM, MD, FACOG, FACS, FAIUM

## Introduction

Assessment of placental location in the mid-trimester fetal anatomic scan is a critical component of sonographic examination as recommended by various national and international guidelines.[1,2] It allows for timely identification of at-risk pregnancies to ensure close surveillance for optimal peripartum management that minimizes maternal and neonatal morbidity and mortality.

Due to varying criteria used at different gestational ages, the true incidence of placenta previa is difficult to determine[3], and at 18 to 23 weeks it has been reported to be around 5% when evaluated by transabdominal scan and 1.5% when evaluated by transvaginal scan.[4] The majority resolve with advancing gestation with a 0.5% incidence reported at term. However, prevalence of placenta previa is on the rise[5] and there are several risk factors for abnormal placentation, at the forefront of which is prior uterine instrumentation, whether it be cesarean delivery, dilatation and curettage or myomectomy. With each cesarean birth, the likelihood of placenta previa in a future pregnancy increases with reported relative risks of 4.5, 7.4, 6.5 and 44.9 for one, two, three and four prior cesarean sections, respectively.[6] The risk is two-fold higher in case of pre-labor cesarean section in comparison to an intrapartum cesarean section.[7] In addition, there are other predisposing factors to placenta previa such as higher-order gestation, advanced maternal age, grand multiparity and pregnancies resulting from assisted reproductive technology.[5,8]

Besides the maternal risks of bleeding antepartum, intrapartum, and postpartum, neonates born to mothers with placenta previa, especially with pregnancy bleeding, are at a higher risk for iatrogenic prematurity as well perinatal morbidity and mortality.[8] In addition, there has been a reported mild increase in intrauterine growth restriction/small for gestational age in neonates from pregnancies with a placenta previa.[9]

A multisociety fetal imaging forum meeting in 2014 defined a low-lying placenta as having the inferior placental

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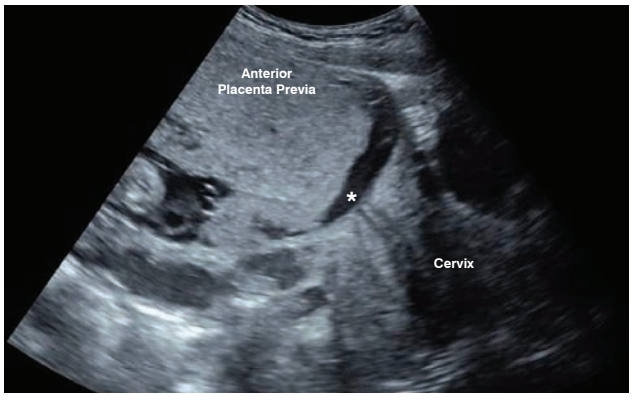



FIGURE 1 Transabdominal examination at 23W1D of an anterior placenta previa shown to completely cover and extend beyond the internal cervical os (*).

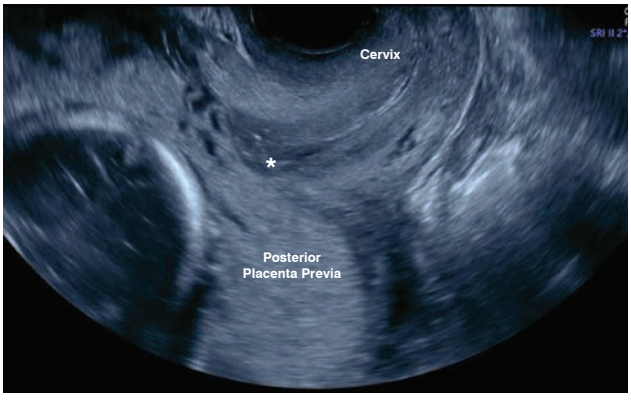



FIGURE 2 Transvaginal examination at 21W5D of a posterior placenta previa shown to completely cover and extend beyond the internal cervical os (*).

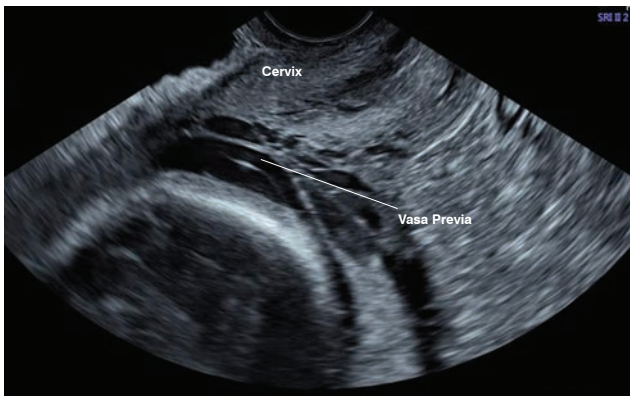



FIGURE 3 Transvaginal examination at 26W6D of a vasa previa shown to completely cover internal os. Note the echolucent lines extending in front of the internal os.

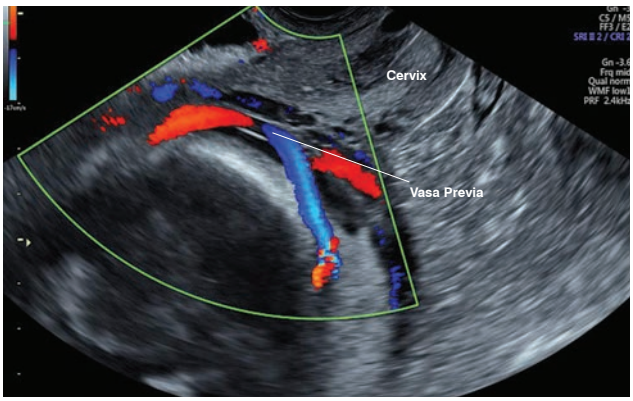



FIGURE 4 Transvaginal examination at 21W5D of a posterior placenta previa shown to completely cover and extend beyond the internal os (*).

edge within 2 cm from the internal os, and a placenta previa where the placenta covers the internal os (Table 1).[10] The forum also recommended abandoning the terms partial and complete placenta previa.

Presence of placenta previa increases risk of placenta accreta spectrum which has added comorbidities. Sonologists should be aware of the increased risk and should take all precautions for diagnosis and proper management of their patients.[8]

The aim of this review is to provide practical tips on diagnosis and management of a placenta previa.

## Role of ultrasound in placental evaluation

The placenta may be visualized as early as 6 weeks by transvaginal sonography and 10 weeks transabdominally. It first appears as a focally thickened hyperechogenic rim of tissue around the gestational sac that is clearly separate from the myometrium. It is quite distinct and easily identifiable at 14 to 15 weeks and the intervillous blood flow may be documented using color Doppler.[3,11]

The relationship between the placental edge and the internal cervical os changes with advancing gestation. As such, it is very important not to label the patient as having a placenta previa prior to 16 weeks.[12] The placenta "migrates" away from the internal os as the lower uterine segment develops and a rate of migration of 5.4 mm per

**TABLE 1 Hallmarks of abnormal placentation on imaging**

| Term | Definition and sonographic signs |
|---|---|
| Low-lying placenta | Inferior edge < 2 cm from the internal os |
| Placenta previa | Placenta covers the internal os |
| Vasa previa | Presence of fetal vessels in front of the internal cervical os |

trimester resolve prior to delivery, at a mean gestational age of 26 weeks, with only 1.6% persisting at term.[14] Though a prior cesarean section[6] and higher parity are risk factors for having a placenta previa, parity does not impact the rate of persistence.[15]

Ultrasound plays a critical role in placental localization whether at the point-of-care setting or during screening examinations. Some of the earliest reports from 1977 suggested that a low lying or placenta previa in early pregnancy may be a normal variant.[16] Though this was initially described transabdominally, the availability of transvaginal scanning since the 1980s has allowed for more accurate diagnoses.[5,17]

Several techniques can be employed to evaluate the placenta, the lower uterine segment, and cord insertion to screen for a placenta previa. It is important to note that presence of a full maternal bladder or uterine contractions may lead to false diagnosis of a placenta previa (Figures 1-4, Table 2).

A simple sonographic technique for placental localization has been described as part of a standardized 6-Step approach for performance of the focused basic obstetric ultrasound exam. The transducer is placed on the midline of the uterine fundus and moved to the lower abdomen in three sweeps (maternal right, left and center). Subsequently, the position of the lower placental edge with respect to the cervix is assessed. If it is less than 2 cm or the placenta is felt to cover the cervix then confirmation by transvaginal scan is indicated.[5]

In case of persistence of a placenta previa into the third trimester, it is critical to assess for possible presence of placenta accreta spectrum. Presence of placental lacunae, loss of the clear retroplacental echolucent space, presence of hypervascularity and bridging vessels, thinning of the myometrium, thinning of the retroplacental myometrial wall and the placental bladder interphase, and a "bulging" placenta into the posterior bladder wall are all concerning findings for a placental accreta spectrum.[8]

> The rate of persistence of a placenta previa is directly related to the gestational age at sonographic diagnosis.

It must be kept in mind that if there were to be normalization of a low-lying placenta or a placenta previa with advancing gestation, it is important to rule out an ensuing vasa previa, which is associated with increased fetal mortality if undiagnosed prenatally. It has been estimated that approximately 28% of prenatally diagnosed pregnancies with vasa previas require an emergent preterm delivery.[19] Presence of echolucent or circular lines overlying the internal os on transabdominal or transvaginal ultrasound should alert the examiner to the presence of vasa previa. This can be confirmed by transvaginal assessment with color and spectral Doppler, confirming presence of arterial fetal vessels.[20,21] Nonetheless, approximately 39% of vasa previas resolve in the third trimester.[22]

Timing of the examination is key to arriving at the correct diagnosis. The rate of persistence of a placenta previa is directly related to the gestational age at sonographic diagnosis. It has been determined to persist in 12% of those diagnosed at 15-19 weeks; 34% at 20-23 weeks; 39% at 24-27 weeks; 62% at 28-31 weeks and 73% at 32-35 weeks.[15] In addition, it is important to keep in mind several tips and tricks when evaluating for a low lying/previa as summarized in Table 2.

## Management

Management of a placenta previa is dictated by gestational age and by whether the patient is bleeding or asymptomatic. Depending on the presentation, inpatient management may be warranted, and it is advisable

to have blood banking capabilities. Ensuring maternal hemodynamic stability and fetal wellbeing are the primary goals. [23]

**As such, there are several considerations for both the clinician and patient to optimize outcomes and minimize risks, primarily those related to iatrogenic prematurity (Figure 5)[24-26]:**

1. Though data are lacking, it is highly advisable to instruct the patient to avoid sexual activity.[27]

2. It is highly advisable to avoid digital examinations.[27]

3. Once a placenta previa is diagnosed at the midtrimester scan, it is recommended to rescan at 32 then 36 weeks for assessment of normalization and for documentation of persistence.[5]

4. In case of normalization, it is important to screen for vasa previa.

5. In some cases, obtaining cervical length in asymptomatic patients may aid in management decisions. It helps identify patients at higher risk for preterm birth who may hemorrhage.[5] Whenever evaluating the cervix, the author recommends utilizing color Doppler to rule out a vasa previa.

6. Though data are inconclusive about the association of a placenta previa with fetal growth abnormalities,[9] close surveillance of fetal growth and antenatal testing as indicated may be a consideration.

7. Every attempt should be made to minimize iatrogenic preterm delivery while taking all precautions in case of bleeding and the need to deliver preterm. In anticipation of a preterm delivery, administration of antenatal steroids (and short-term tocolysis if safe for 48 hours) should be prioritized primarily in case of vaginal bleeding at 24 to 34 weeks.[8]

8. It is important to correct maternal anemia and to administer Anti-D when indicated following a Kleihauer-Betke test for proper anti-D dosing.[8]

9. Screening the patient for a possible placenta accreta spectrum, especially in the setting of prior cesarean deliveries, while taking all the necessary steps required for intraoperative management, is paramount.[8]

10. Consultation with the neonatology team should be arranged to have the family discuss their wishes with the neonatology team, particularly in cases of peri-viability.[8]

11. In case of cessation of vaginal bleeding for over 48 hours and where the patient is dependable and has reliable means of transportation, outpatient management is a consideration.[8]

12. There is no evidence to support prophylactic cerclage in patients with a placenta previa.[8]

13. Timing of delivery is dependent on several factors although an early-term birth at 36 to 37 6/7 weeks is recommended,[24,25] without the need to verify fetal lung maturity via amniocentesis,[24] to optimize maternal and neonatal outcomes. [28]

14. There is no evidence to support the need for general versus regional anesthesia in patients with a placenta previa and that should be left to the discretion of the anesthesiology team.[8]

**TABLE 2 Imaging tips and tricks**

| | |
|---|---|
| Timing of examination | Mid-trimester fetal anatomy scan starting at 16 weeks |
| Patient preparation | Empty bladder |
| Route of scanning | Transabdominal (Figure 1) examination, however, if suspicious then transvaginal examination (Figure 2) |
| Machine settings | Optimize overall settings for cervical assessment and the color Doppler settings for placental vascularity |
| Optimal planes | Sagittal planes. Avoid a diagnosis in the presence of a full bladder or with a uterine contraction |
| Other modalities | If a vasa previa is suspected (Figures 3 and 4), employ spectral wave Doppler to confirm presence of arterial fetal vessels |
| Sonographic clues to diagnosis | Low inferior placental edge<br>High presenting fetal part |
| Sonographic clues to persistence | Placenta extends over and beyond the internal os<br>Persistence at 32 weeks |

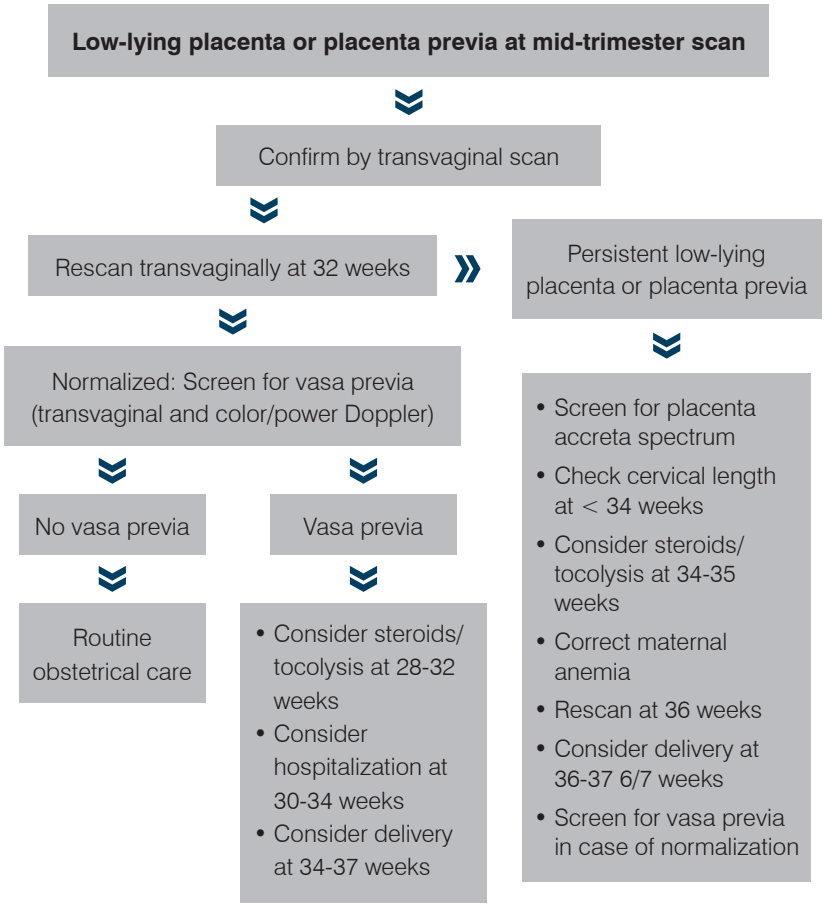
## Conclusion

Incidence of placenta previa is on the rise and is directly related to the number of prior cesarean sections. It leads to serious maternal and neonatal morbidity and mortality. Screening all patients and properly determining placental location, using transvaginal sonography beyond 16 weeks' gestation, is critical to avoid causing undue parental anxiety by prematurely diagnosing a placenta previa in early gestation. Ob/gyns should be aware of placental migration and normalization of a placenta previa with advancing gestation. In case of normalization, it is important to screen for vasa previa. In case of persistence, precautionary steps should be taken to safeguard both mother and baby. Vigilance, a systematic approach, and following a standardized protocol help ensure optimal outcomes. ■

**DISCLOSURES** The author reports no potential conflicts of interest with regard to this article.

**FOR REFERENCES VISIT**
**contemporaryobgyn.net/PlacentaPrevia**

## FIGURE 5 MANAGEMENT ALGORITHM

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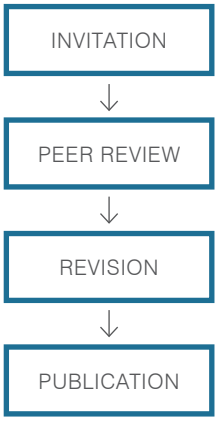

# Birth outcomes in impoverished areas of the US

*by* JUDITH M. ORVOS, ELS

A new report from the Centers for Disease Control and Prevention (CDC) shows that mothers and their babies in Appalachia and the Delta have worse outcomes than their counterparts elsewhere in the United States. The findings are based on analysis of 2017 birth certificate data and 2016-2017 linked birth/infant death data from the National Vital Statistics System.

Published in *National Vital Statistics Reports,* the analysis provides insight on Appalachia and the Delta, two of the most economically disadvantaged areas of the country. Appalachia includes all of West Virginia and parts of 12 other states; the Delta is composed of eight states: Alabama, Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee.

The authors looked at three infant outcomes: preterm birth (PTB), low birthweight, and infant mortality. Maternal characteristics assessed included race and Hispanic origin; age; marital status and paternity acknowledgement; education; receipt of assistance from the Special Supplemental Nutrition Program for Women Infants, and Children (WIC); source of payment for delivery; smoking; body mass index (BMI); and timing of prenatal care.

The 124,047 births to women in the Delta and 275,493 births to women in Appalachia in 2017 accounted for 3.2% and 7.2% of all births during that period nationwide. Fifty-three percent of Delta women who gave birth in 2017 were non-Hispanic white and 37.5% were non-Hispanic black, versus 75.6% and 11.6% of mothers in Appalachia, respectively. In the rest of the country, 49.7% of women were non-Hispanic white and 14.0% were non-Hispanic black. Of the women who gave birth in the Delta, 36.5% were under age 20, versus 31.7% of the women in Appalachia and 24% of those in the rest of the country.

Infants in the Delta were more likely to be delivered preterm (12.37%) or low birthweight (10.75%) and were more likely to die in their first year of life (8.17 infant deaths per 1,000 live births) than those born in Appalachia (10.75%, 8.87%, and 6.82, respectively), while those born in the rest of the United States were the least likely (9.78%, 8.14%, and 5.67, respectively).

Confounding factors that were evaluated included education, insurance coverage, and start of prenatal care. The authors found that among women aged 25 and over, those in the Delta were more likely to have a high school education or less (36.0%) than women in Appalachia (32.4%) versus 29.2% of women in the rest of the country. Of deliveries in the Delta, 59.7% were covered by Medicaid, versus 46.2% in Appalachia and 42.2% in the rest of the country. Of the mothers in Appalachia, 15.2% smoked, versus 10.2% of those in the Delta and 6.1% in the rest of the country. Nearly 75% of women in the Delta did not begin prenatal care in the first trimester, versus 77.2% in Appalachia and 77.4% in the rest of the country. ■

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

**SOURCE**
Driscoll AK, Ely DM. *National Vital Statistics Reports.* US Department of Health and Human Services; 2019. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_11-508.pdf.

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# Late pregnancy sleep position and birthweight

Risk of stillbirth is known to be elevated in women who go to sleep supine late in pregnancy. A new study suggests that doing so also may be associated with lower birth weight in offspring.

*by* JUDITH M. ORVOS, ELS

Published in *JAMA Network Open*, the findings are from a prespecified subgroup analysis of data from the controls in four case-control studies on sleep and stillbirth in New Zealand, Australia, and the United Kingdom. The participants were all women with ongoing pregnancies at 28 weeks' gestation or more.

The primary outcome examined by the investigators was adjusted mean difference (aMD) in birth weight. They also assessed birth weight centiles and adjusted odds ratios (aORs) for birth weight < 50$^{th}$ and < 10$^{th}$ centile (small for gestational age [SGA]) for supine vs. non-supine going-to-sleep position in the last 1 to 4 weeks, adjusted for variables known to be associated with birth size.

The authors calculated the centiles for the population according to INTERGROWTH-21$^{ST}$ and customized centiles. INTERGROWTH-21$^{st}$ centiles are a birth standard derived from a low-risk birth cohort and adjusted for gestation at birth and infant sex. The customized birth centiles, based on a fetal growth standard, also are adjusted for gestation at birth and infant sex as well as other variables.

A woman's going-to-sleep position was defined as her usual position over the previous week, 2 weeks or month and varied by study. Position as recorded as left or right side, supine and other. Supine was compared with non-supine in the main analysis and all four positions were assessed in the secondary analysis.

The researchers compared infant birth weight and birth weight centiles by maternal going-to-sleep position. Adjustments were made to gestational age at birth, infant sex, maternal age, and other factors such as preexisting diabetes and hypertension. Multivariable analyses also were adjusted for individual studies as a covariate.

Of the 1760 women in the studies, 3.2% said they usually slept supine in the previous 1 to 4 weeks. Adjusted mean (SE) birth weight was 3410 (112) g in women who reported the supine position and 3554 (98) g in women who slept non-supine (aMD, 144 g; 95% confidence interval [CI] -253 to -36g; $P = .009$). That equated to a 10-percentile reduction in adjusted mean INTERGROWTH-21$^{st}$ and customized centiles. Going to sleep supine also was associated with a three-fold increase in SGA by INTERGROWTH-21$^{st}$ standards (aOR, 3.23; 95% CI, 1.37-7.59) and a nonsignificant increase in SGA customized standards.

The authors noted that supine maternal position is associated with a reduction in maternal cardiac output and subsequent fetal blood supply, so, "it is biologically plausible that supine maternal going-to-sleep position could contribute to reduced birth size. Our finding of an independent mean reduction in birth weight associated with supine going-to-sleep position is clinically relevant." They said that theirs is the first study to identify an association between supine maternal sleep position and lower birth weight in women with ongoing pregnancies in a high-income setting. ■

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

**SOURCE**
Anderson NH, Gordon A, Li M, et al. Association of Supine Going-to-Sleep Position in Late Pregnancy With Reduced Birth Weight. *JAMA Network Open*. 2019;2(10). doi:10.1001/jamanetworkopen.2019.12614

*Read more about pregnancy management on* PAGE *12*

# Preterm birth phenotypes in women with autoimmune disease

*by* **BOB KRONEMYER**

Women with autoimmune rheumatic diseases have an elevated risk of various preterm birth (PTB) phenotypes, according to a large population-based, retrospective cohort study. Hence, the study in *BJOG* strongly advocates preconception counseling and close monitoring during pregnancy.

All live singleton births in California between 2007 and 2011 were analyzed, representing maternally linked hospital and birth certificate records of 2,481,516 deliveries. Patients with five prevalent autoimmune rheumatic diseases at the time of delivery were identified by ICD-9 codes: systemic lupus erythematosus (SLE) (n = 2,272); systemic sclerosis (SSc) (n = 88); rheumatoid arthritis (RA) (n = 1,501); polymyositis/dermatomyositis (DM/PM) (n = 38); and juvenile idiopathic arthritis (JIA) (n = 187).

PTB was defined as birth between 20 weeks and less than 37 gestational weeks, based on the obstetric estimate. It was also subcategorized by gestational age: early (20 to less than 32 weeks) and late (32 to less than 37 weeks). PTB was due to either preterm premature rupture of membranes (PPROM), spontaneous, or medically indicated.

The investigators compared patients with autoimmune disease to the general obstetric population, while adjusting for maternal age, race/ethnicity, body mass index (BMI), smoking, education, payer, parity and prenatal care.

Patients with autoimmune disease had an increased relative risk (RR) for PTB for each of the five autoimmune diseases evaluated: SLE (RR 3.27; 95% confidence interval [CI]: 3.01 to 3.56); RA (RR 2.04; 95% CI: 1.79 to 2.33), SSc (RR 3.74; 95% CI: 2.51 to 5.58); JIA (RR 2.23; 95% CI: 1.54 to 3.23); and DM/PM (RR 5.26; 95% CI: 3.12 to 8.89).

Multiparous women with SLE had a higher risk of preeclampsia than nulliparous women.

"These elevated risks were observed for the majority of preterm birth phenotypes as well," wrote the authors from Stanford University School of Medicine.

At least 90% of the women with maternal autoimmune disease started prenatal care within the first 5 months of pregnancy and were nonsmokers. In addition, 64.7% of these women were nulliparous. Furthermore, women with autoimmune diseases were more likely to be non-Hispanic White, with the exception of those with SLE.

Women with autoimmune diseases also had a higher incidence of pre-existing hypertension, pregnancy-induced hypertension, pre-existing diabetes and gestational diabetes compared to the general obstetric population. However, for SLE, the rate of gestational diabetes was similar for the two groups: 7.22% vs. 7.17%.

But women with SLE had a higher risk for early overall PTB, as well as for medically indicated and spontaneous PTB, compared to corresponding late PTB phenotypes. Women with DM/PM and SSc also trended toward a comparable higher risk for many early preterm phenotypes as opposed to late preterm phenotypes.

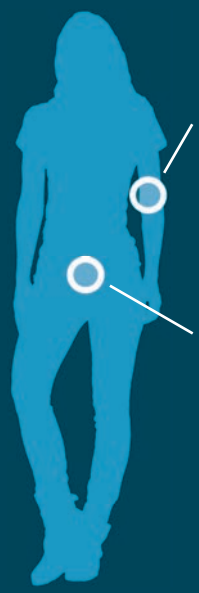
For the autoimmune disease cohort as a whole, the frequencies of preeclampsia/eclampsia; small for gestational age/intrauterine growth restriction; and a placental abruption, complicated medically indicated preterm birth were 21.4%, 16.2% and 3.9%, respectively.

Furthermore, the relative risk of any form of preeclampsia was significantly elevated for each of the five autoimmune diseases, with risk of severe preeclampsia particularly high among women with SLE (RR 4.5; 95% CI: 3.7 to 5.4) and with SSc (RR 6.1; 95% CI: 2.7 to 13.5). Multiparous women with SLE also showed a higher risk of preeclampsia than in nulliparous women.

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

**SOURCE**

Kolstad K, Mayo J, Chung L, et al. Preterm birth phenotypes in women with autoimmune rheumatic diseases: a population-based cohort study. BJOG. 2019. doi:10.1111/1471-0528.15970




# Help your patients understand both of their LARC location options[1]

IUD, intrauterine device; LARC, long-acting reversible contraceptive.

NEXPLANON is indicated for use by women to prevent pregnancy.

## SELECTED SAFETY INFORMATION

**Who is not appropriate for NEXPLANON**

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

**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.



US-XPL-00588 05/19

# NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Up to **3 years** of pregnancy prevention*

**>99%** effective†

**Reversible** if her plans change

Placed subdermally just under the skin in the inner upper arm

*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.

(Actual implant shown; actual implant is 4 cm)

## SELECTED SAFETY INFORMATION *(continued)*

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

**Counsel her about changes in bleeding patterns**

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

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

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

**Please read the adjacent Brief Summary of the Prescribing Information.**

**Reference:**

**1.** American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol.* 2017;130(5):e251–e269.

MERCK

# 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.

# Nexplanon®
(etonogestrel implant) 68mg

**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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# Uterine allografts: A new era in reproduction

Pioneers in uterine transplantation provide an update on an investigational procedure that holds promise for women with absolute uterine factor infertility.

*by* TOMMASO FALCONE, MD, FRCSC, FACOG, AND REBECCA FLYCKT, MD

Uterine transplantation (UTx) has rapidly moved from a theoretical construct to a clinical reality. Over just the past 5 years, the world has witnessed several notable milestones in this quickly-evolving field. With healthy live birth being the ultimate goal of a reproductive transplant, the 14 babies born to date following UTx for which reports exist and the additional ongoing pregnancies represent proof of concept for the viability of this experimental procedure.

## Options for AUFI

UTx represents the first and only treatment for women with absolute uterine factor infertility (AUFI). AUFI can be either congenital (e.g., Mayer Rokitansky Kuster Hauser syndrome) or acquired. Estimated to affect one in 500 women, AUFI has previously only been addressed using in vitro fertilization (IVF) with gestational carriers, fostering, adoption, or planning a life without children.[1] For some women, these may be acceptable options, but for others, these alternatives may not be desired, often due to personal, social, cultural or religious beliefs. Choices for women with AUFI are especially limited in parts of the world where gestational carriers and even adoption may be socially unacceptable, highly restricted, or banned completely. Interviews of women with AUFI in a uterine transplant trial indicate that the diagnosis of AUFI can be a devastating and life-altering experience and that achieving reproductive autonomy is a key desire of women with this condition.[2]

## AUFI Milestones

The advent and rapid ascent of UTx have been marked by innovation. Initial international attempts in humans performed outside of clinical trials were not successful, and technical success for the Swedish team was ultimately achieved following decades of preparatory work in small mammals and non-human primates. As with any new surgical procedure, the technical elements have quickly advanced and evolved (Table 1).

Together with documented technical success and increased media attention has come improved public perception and enhanced physician awareness and support for the procedure. Sixty percent of American Association of Gynecologic Laparoscopists (AAGL) and American Society for Reproductive Medicine (ASRM) members sup-

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**TABLE 1 Landmark events in UTx**

| | |
|---|---|
| 2015 | • First reported birth from living donor UTx[3] |
| 2016-2018 | • Multiple uterine transplant trials announced internationally[1,4,5] |
| 2017-2018 | • Variations for graft outflow with use of ovarian/utero-ovarian vessels[6-8]<br>• Laparoscopic and robotic techniques for graft procurement in living donors[6-8] |
| 2019 | • First birth from a deceased donor uterus[9] |

port UTx as a treatment for AUFI.[10] A 2018 study of public perception of UTx in the United States indicated that 78% of respondents supported UTx and 45% believed it should be covered by insurance.[11] Another recent study indicated that 74% of women would donate their uterus for transplant.[12] It is unclear what the cost of a uterine transplant will be, and how or whether insurance will cover this reproductive procedure. As the discussion evolves along with the science, questions regarding access, cost, and safety will be paramount.

Slow initial acceptance of UTx may be due to the fact that, unlike other transplants, UTx is not a life-saving transplant. Like face, hand, and other vascularized composite allographs, the uterine transplant can be life-enhancing and indeed can be life-giving. Also distinct from other known organ transplants, UTx is an "ephemeral" transplant.[13] This means that the uterus will be removed after one or two live births are achieved and is not intended to be a lifelong transplant. This means that women receiving a UTx will not be exposed to immunosuppression once the uterus has been removed after childbearing.

Despite growing numbers of live births, UTx remains a significant undertaking for both recipients and living donors. The procedure for donor hysterectomy is similar to radical hysterectomy, and donor complications have been reported in the literature.[14,15] Historically, donor surgeries have involved long operating room times (10-13 hours in the original Swedish series) and large incisions, although this may change as laparoscopic and robotic approaches are pioneered. Although a deceased donor model obviates this risk completely, most live births to date have been achieved with living donors. Deceased donor UTx represents a more ethical choice by eliminating donor risk, however, it has the limitations of organ availability, less convenient scheduling, and more restricted medical history on the donor.[1] It is unknown how outcomes from deceased donor trials will compare with living donor trials and whether one approach will demonstrate superiority over the other or whether both approaches will coexist. Recent studies suggest no recipient preference for a living vs a deceased donor.[2]

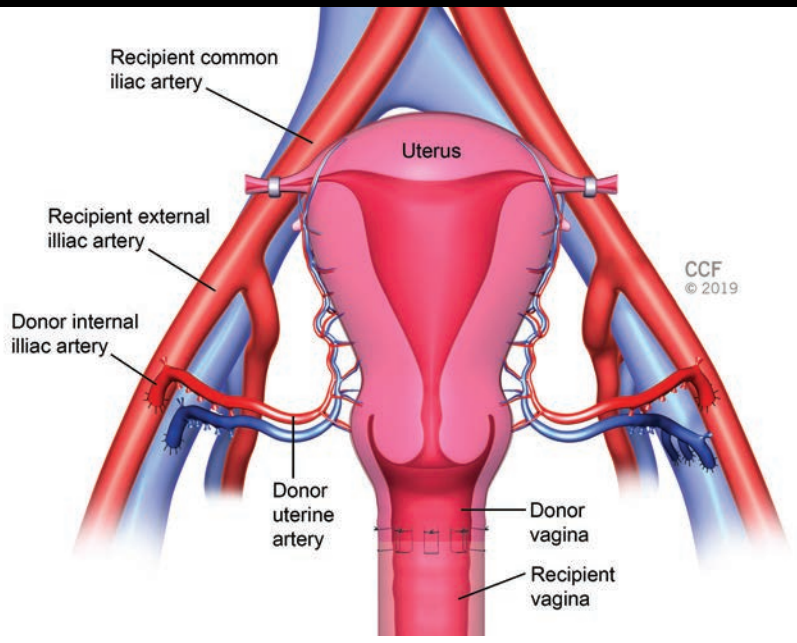
It is unclear what the cost of a uterine transplant will be and whether insurance will cover this reproductive procedure.

## Risks of UTx

Risks to the recipient are also currently being determined in clinical trials. The major risk is hysterectomy, due to either infection or graft thrombosis. Although data on clinical outcomes and complication rates are still very limited, in the original Swedish trial, two of nine patients (22%) required hysterectomy prior to attempted embryo transfer.[5] After IVF to create embryos and listing for transplant, the recipient must undergo three or four separate major abdominal procedures including uterine implantation, cesarean delivery (possibly x 2), and then hysterectomy to remove the graft. In addition, immunosuppression in the recipient carries risks and side effects during treatment that a young and healthy woman would not normally need to manage. Registries of pregnancy with other solid organ transplants have supported the safety of the immunosuppressive regimens used for UTx in relation to fetal and neonatal well being.

Careful screening, selection and counseling of UTx recipients and their families is necessary in the context of a clinical trial. As such, a UTx team must consist of a broad range of subspecialists at an academic center with a capability for longitudinal follow-up (Table 2). At this point, uterine transplant is still experimental and should only be conducted under

**FIGURE 1** Schematic of deceased donor uterine graft with vascular and vaginal anastomoses in typical configuration.




an IRB-approved research program.[16] As "success" with uterine transplant has multiple endpoints (graft viability, onset of regular menses, and embryo implantation, pregnancy, and ultimately delivery of a healthy neonate) that may occur over several years, a multidisciplinary team must be in place that can conduct years of surveillance of mothers and infants.

## Technical considerations

Many aspects of a UTx program are complex, but by far the most challenging aspect is surgical retrieval of the uterus and implantation of the graft into the recipient. Development of safe surgical techniques that optimize graft performance is of great interest within clinical trials of UTx, including our own at the Cleveland Clinic. A successful graft (whether from a living or deceased donor) must have adequate circulatory inflow and outflow. This optimizes functionality and prevents ischemia and thrombosis, which are major causes of graft failure worldwide in UTx.[13] A well-functioning graft will be able to tolerate the increased demands of uterine blood flow during pregnancy, which represents one-sixth of the cardiac output. Preventing infection and rejection are also key considerations in the perioperative and post-transplant period.

In a living donor model, obtaining adequate vascular support for the transplanted uterus must be balanced against potential risky dissections in the deep pelvis, which can compromise the ureter, nerves, or blood vessels in this area of the donor. Genitourinary complications have been reported in living donor trials from Sweden, Texas, and Saudi Arabia.[14,15] The major difficulty is complex dissection of the uterine vessels, notably the branching uterine veins that lie in proximity to the ureter. Due to these concerns and reported injuries, the exclusive use of the utero-ovarian vein has been successfully applied and has resulted in a live birth in the United States.[14] Use of these kinds of vessels has made an easier transition to development of laparoscopic and robotic approaches as well.[6-]

## The future of UTx

Given the rapid pace of the last 5 years, what will the next decade hold for this dynamic and innovative field? We anticipate ongoing progress and refinements in the spirit of innovation that characterized development of this reproductive procedure. Living donor surgeries are already becoming shorter and less risky, involving more minimally invasive techniques such as robotics and laparoscopy and innovative vascular support that avoids extensive

**TABLE 2** Recommended composition of a uterine transplant team

- Transplant surgery
- Gynecologic surgery
- Reproductive endocrinology and infertility
- Maternal-fetal medicine
- Neonatology
- Bioethics
- Psychology
- Social work
- Additional disciplines: Infectious Disease, Radiology, Pathology, Anesthesia

We anticipate reduced immunosuppressive regimens and shorter times to embryo transfer to reduce exposure to immunosuppression.

pelvic dissections in donors. Women (mothers, sisters and friends) should not have to feel pressure to undergo lengthy and potentially risky surgeries to help alleviate suffering of a loved one with AUFI. We can envision that donor procurement may evolve to a 4- to 6-hour completely minimally invasive hysterectomy with a one-night hospital stay and relatively low risk of complications. However, in pursuit of minimally invasive approaches using the ovarian vessels, we must be cautious to avoid removing the ovaries in donors, as this can have significant long-term health consequences.[17]

In deceased donor studies, we anticipate additional live births from our center and others. With more births from deceased donor transplants, we will be able to more directly compare outcomes related to deceased versus living donor models. Further bioethical analysis will be needed to consider risks to mothers, offspring, and donors/donor families. Reducing ischemia time and increasing the availability of suitable donor uteri (e.g., using "increased-risk" donors, widening recovery radius), and enhancing preservation and perfusion techniques to reduce the effects of ischemia are key areas of interest.

For recipients, we anticipate reduced immunosuppressive regimens and shorter times to embryo transfer to reduce exposure to immunosuppression. As additional reassuring data on obstetrical and neonatal wellbeing emerge, we anticipate more widespread understanding and acceptance among physicians and the general public. International organizations such as the International Society for Uterine Transplantation (ISUTx) have fostered collaborations between research centers[18] with the recent annual meeting at the Cleveland Clinic in September 2019; a registry is forthcoming to more rigorously collect data regarding procedures and outcomes. Looking ahead, as experimental trials will have limited funding for UTx and there is ongoing demand, we hope to expand access by continuing discussions with the public, employers, and insurance companies regarding cost and coverage for the surgical correction of an otherwise incurable condition that carries significant personal, marital, and social harm.

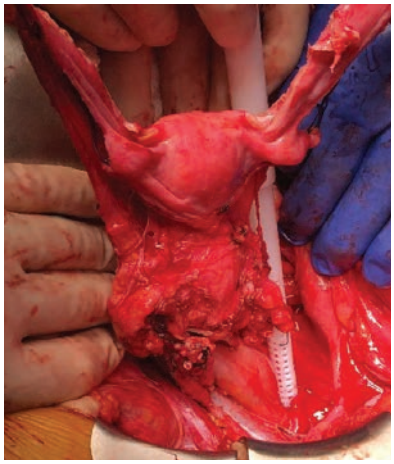


**FIGURE 2** Deceased donor uterine transplant graft perfusing after reimplantation.

Further areas for future discussion will include options for spontaneous pregnancy with tubal transplant along with the transplanted uterus, the likely emergence of uterine transplant for trans women, and the possibility of a bioengineered uterus or uterine xenotransplantation.

## Conclusion

Although UTx remains a technically challenging and complex undertaking, our comprehension of this procedure has made extraordinary progress in a very brief time. Insights and basic science efforts for UTx research extend beyond uterine transplantation itself; in doing this work we may begin to apply our understanding to mechanisms of embryo implantation, early pregnancy and uterine receptivity, reproductive and placental immunology, and numerous other aspects of obstetrics and gynecology. Although the field is still early in its evolution, UTx is leading us into a new and exciting era of reproductive transplantation which has wide-ranging applications. ■

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**FOR REFERENCES VISIT**
**contemporaryobgyn.net/UterineAllografts**

# Endometriosis for the generalist

For a chronic condition like endometriosis, it is important to develop the physician-patient relationship into a partnership.

*by* MOBOLAJI O. AJAO, MD, MPH

Endometriosis is the presence of endometrial-like glands and stroma outside the uterus. It is a common cause of abdomino-pelvic pain, adnexal mass, and infertility in reproductive-age women. Endometriosis affects an estimated 10% to 20% of reproductive-age women and up to 70% to 90% of patients with chronic pelvic pain.[1-3] Several theories exist regarding the pathogenesis of endometriosis, with the most widely accepted being Sampson's retrograde menstruation.[4,5] However, all theories have gaps, thus the exact pathophysiology of endometriosis remains enigmatic.

Although hormonal management and surgery offer symptomatic relief, a cure for endometriosis continues to be elusive. Maneuvering through obstetric care, annual gynecologic visits, and the myriad of problem visits in a busy generalist practice is already challenging, and undertaking a thorough evaluation and management of endometriosis often leads to frustration to both patient and provider.

## Initial evaluation

Ob/gyns should be prepared to have a lasting relationship with women with endometriosis because the condition is chronic and has no known cure. It is important to bear in mind that most patients have been dealing with pain for years prior to diagnosis, with a mean time of 7 to 11 years delay in diagnosis of endometriosis.[6] The common 15- to 20-minute allotted time for a new patient consult will be wholly inadequate for an initial evaluation. To expect to review the pages of outside records that patients often have, obtain a comprehensive history, perform a detailed exam, and initiate an assessment/plan in this limited time is a set-up for patient and physician dissatisfaction.

Some changes to practice and communication go a long way. If possible, schedule all new pelvic pain or endometriosis consults for 30 minutes. When patients are scheduling their appointments, they should be asked to send any records over for review prior to the consult. This allows for focusing on the visit rather than scanning rapidly through pages of records during the allotted time.

It is important to acknowledge the patient's symptoms and the fact that they may have been present for a long time, while noting that it is unlikely that a solution will be available at the first consult. If outside medical records

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are available and have been reviewed, let the patient know that you have thoroughly reviewed them and are familiar with the location of her pain, aggravating factors, and prior medical and or surgical management. This allows for a focused and guided history that optimizes the consult time.

If a detailed history of a patient's symptoms is not available via outside records, then ask her about cyclic/noncyclic pain, pain with urination, pain with bowel movements, presence and site of pain with intercourse, bloating, fatigue, and disruptions in quality of life. Questions should also be asked to discern other potential causes of pelvic pain, including non-endometriosis gynecologic pain, gastrointestinal, urinary tract, musculoskeletal, psychological, and neurologic. Follow this with a detailed abdominal and pelvic exam. The pelvic exam should include a Q-tip evaluation of the vulva, single-digit vaginal exam to assess levator ani, obturator internus, piriformis, bladder, urethra, vaginal fornices, and uterosacral ligaments. A bimanual exam should then be performed, followed by a rectovaginal exam. Sometimes due to time constraints or inexperience with pelvic pain-centered exam, the pelvic exam portion of a patient's note is normal and reads like a standard template. While this may, in fact, be the case, pertinent negatives of the exam components described above should be included.

## Imaging

Imaging of the pelvis can be used to rule out other causes of abdomino-pelvic pain, elaborate abnormal findings on exam, or to assess for endometriotic involvement of structures not palpated during the exam. The two common imaging modalities used in endometriosis imaging are pelvic ultrasound and magnetic resonance imaging (MRI). Pelvic ultrasound is the initial modality of choice because of its wide availability, relatively low cost, and utility for simultaneous assessment of pelvic structures and virtual diagnosis of most ovarian endometriomas.[7]

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affects an estimated
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When pelvic exam or ultrasonography suggest advanced disease, i.e. deep infiltrating endometriosis (rectovaginal or uterosacral nodularity), some experts choose to order a pelvic MRI. This is done to determine the extent of deep infiltrating endometriosis and assess for rectovaginal nodules and bowel wall, bladder or ureteral involvement. Transvaginal ultrasound and pelvic MRI have been compared for their ability to identify deep infiltrating endometriosis, with both performing similarly. For MRI detection of rectosigmoid endometriosis, sensitivity was 85% (95% CI, 0.78-0.90) and specificity was 95% (95% CI, 0.83-0.99), while for transvaginal ultrasound, sensitivity was 85% (95% CI, 0.68-0.94), and specificity was 96% (95% CI, 0.85-0.99).[8] For MRI detection of rectovaginal endometriosis, sensitivity was 66% (95% CI, 0.51-0.79) and specificity was 97% (95% CI, 0.89-0.99), while for transvaginal ultrasound, sensitivity was 59% (95% CI, 0.26-0.86) and specificity was 97% (95% CI, 0.94-0.99). For MRI detection of uterosacral ligament endometriosis, sensitivity was 70% (95% CI, 0.55-0.82) and specificity was 93% (95% CI, 0.87-0.97), while for transvaginal ultrasound, sensitivity was 67% (95% CI, 0.55-0.77) and specificity was 86% (95% CI, 0.73-0.93).[8] It is important to note that while transvaginal ultrasound offers the advantage of dynamic imaging with pain- or tenderness-guided scanning, it is operator-dependent with expert guided transvaginal ultrasound performing better than routine scans.[9] MRI has the advantage of imaging the abdomen and pelvis, assessing for endometriosis in less common sites (small bowel, appendix, abdominal wall), and has a reproducible protocol. Despite this performance, definitive diagnosis of endometriosis is surgical, preferably with laparoscopy. Presumptive diagnosis can be made without laparoscopy when typical symptoms are present, and patients can be started on medical management.

## Management

By the time most patients see a gynecologist for pelvic pain that later will be diagnosed with endometriosis, they have usually been on the first-line agent for pelvic pain, namely a nonsteroidal anti-inflammatory drug (NSAIDs). It is important to evaluate for and rule out other causes of pelvic pain before starting other therapies for a presumptive diagnosis of endometriosis.

Endometriotic implants express hormone receptors, explaining the plausibility of hormonal suppression. There

Both leuprolide and continuous OCs help decrease pain in women with endometriosis, however, continuous OCs are considerably cheaper.

are several hormonal formulations available for managing endometriosis-related pain, including oral contraceptives (OCs), progestins, danazol, gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, and aromatase inhibitors (AIs). It may be easier to divide these into first- (OCs and progestins), second-(danazol, GnRH agonists, and GnRH antagonists), and third-line agents (AI). A detailed patient history should identify comorbidities that may preclude use of certain classes of hormones in some women, such as migraines with aura, thrombosis, hypertension, and smoking status.

Given the invasiveness of diagnostic laparoscopy, patients are often given a trial on NSAIDs and first-line agents for several months before surgery is considered. It is also reasonable to continue patients on these drugs after surgery. Although a variety of combined OC formulations are available and data support improvement in endometriosis pain,[10] they do not support a benefit of one agent over another.

Treatment can be started with a 20-µg ethinyl estradiol formulation, with titration up to a 35-µg pill as necessary. While patients are often initiated on cyclic use of combined OCs, they can be used in a continuous fashion. Both schedules have been shown to decrease pain, with an edge towards continuous use.[11,12] Available progestins include oral formulations such as the progestin-only pill (norethindrone 35 µg), norethindrone acetate 5 mg; depot medroxyprogesterone acetate, and the levonorgestrel intrauterine system. All of these have shown improvement in patient pain[13-17] and the limiting factors will often be patient preference, cost, and tolerability or side effect profile. Norethindrone acetate can be titrated to 10 or even 15 mg daily, but caution should be exercised if it is used for extended periods as it can adversely affect lipid levels. Side effects most often reported with progestins include weight gain, bloating, irregular bleeding, and mood changes. Depo provera carries risk of bone loss, but less than for GnRH agonists.[14]

Second-line agents can be used if a patient's endometriosis fails to respond to a trial of first line agents or for postoperative medical suppression. GnRH agonists such as Leuprolide acetate for depot suspension (monthly or 3-monthly), the most common second-line agent, or daily intranasal nafarelin have been shown to decrease endometriosis-related pain and can be offered to patients.[18-20] There is often some hesitancy in using these agents, given their significant side effect profile. Leuprolide acetate can be administered for 6 months without add-back or up to 12 months with add-back therapy, with daily oral norethindrone acetate 5 mg being the most commonly used add-back. The add-back limits the adverse effects on bone density and lessens vasomotor symptoms. Both leuprolide and continuous OCs achieve similar pain decreases in women with endometriosis, however, continuous OCs are considerably cheaper.[19]

The US Food and Drug Administration approved Elagolix, the first GnRH antagonist, in August 2018 after it demonstrated improvement in dysmenorrhea and non-menstrual pelvic pain in women with surgically diagnosed endometriosis.[21] Two doses are available: 150 mg daily for 24 months and 200 mg twice daily for 6 months. Dyspareunia was improved on the higher dose. This agent adds to the armamentarium of medical therapy for endometriosis, but it is still quite new in clinical practice and there remain some insurance and prior authorization barriers.

Danazol is an oral agent with high androgenic activity and related side effects including weight gain, decreased breast size, acne, hirsutism, deepening voice, and abnormal liver function tests.[22] It is rarely used in practice nowadays, given the side effect profile and availability of other options.

AIso, the third-line group of agents, are considered experimental and usage is typically in consultation with providers experienced or specializing in medical management of endometriosis. Certain factors have been associated with diagnosis of laparoscopy- confirmed endometriosis and are thus possibly amenable to lifestyle modifications. Missmer et al noted a higher incidence of laparoscopically-confirmed endometriosis in women with increased consumption of transfat and low intake of omega 3 fatty acids.[23] Risk of endometriosis was lower in women who consumed foods rich in thiamine, folate, vitamin C, and vitamin E, but that was not the case with consumption of those supplements alone.[24] Consumption of fresh fruits and green vegetables was also associated with a lower risk of endometriosis, while intake of red meat was associated with a higher risk.[25]

## Surgery

The appropriate time to offer surgery will vary based on patient presentation, namely persistent pain, fertility evaluation, or abnormal imaging findings. Diagnostic laparoscopy should be offered to a patient with a presumptive diagnosis of endometriosis who has persistent pain despite 6 months of NSAIDs and first-line hormonal agents. Naturally, if large symptomatic endometriomas or deep infiltrating endometriosis are noted, surgery is also recommended.

In the setting of a normal clinical exam and unremarkable imaging, it is important to discuss the possibilities of negative laparoscopy and also minimal-to-no change in pain following surgery. In the setting of significant deep infiltrating endometriosis, usually of the rectosigmoid or rectovaginal septum, it is equally important to have a preoperative discussion with the patient about the extent of surgery and excision as well as the associated surgical morbidity. This shared decision-making might reveal how aggressive a patient wants her procedure to be, a particularly important point, as the disease occurs in mostly otherwise healthy women. The notion of a bowel resection might be comprehensible for postmenopausal ovarian cancer, but not necessarily for a benign condition like endometriosis in a young patient, despite its significant impact on quality of life. That being said, the goal of surgery should be to offer a diagnosis and to address all endometriosis present.

The most widely used staging system for endometriosis is the revised ASRM classification.[26] Visually, endometriosis has been described with various appearances, from vesicular, clear, red, blue, brown, powder burn, fibrotic, to Allen-Masters peritoneal defect. While many providers rely solely on visual diagnosis before proceeding to destroy endometriotic lesions, it is important to note that correct visual diagnosis of endometriosis, especially stage I disease, can be as low as 50%.[27]

The gold standard for diagnosis should be histology, not visual. It is advisable to perform an exam under anesthesia as relaxation of the pelvis allows for a detailed exam that is often more accurate than in the clinic setting. Another tip in refining and improving exams performed in the clinic is to repeat one after laparoscopic visualization of lesions. For example, if a uterosacral nodule is noted on laparoscopy, perform a digital vaginal and rectovaginal exam under laparoscopic view. This offers unique real-time feedback about where the pelvic hand needs to be for a correct uterosacral examination. The same is true for rectovaginal nodules. It is important to know how high or low nodules are from the anal verge and the relation of nodules to the pouch of Douglas, posterior cervix, and lower pelvic sidewall. Unfortunately, pneumoperitoneum will prevent adequate bimanual examination of the adnexa while under laparoscopic vision. Performing these exams habitually will lead to improved accuracy in exams performed in the office.

> A tip for refining and improving exams performed in the clinic is to repeat one after laparoscopic visualization of lesions.

For superficial peritoneal lesions encountered during laparoscopy, either excision or ablation of endometriosis can be performed as studies suggest that pain outcomes are similar.[28,29] In patients who have had prior laparoscopy with pathology-confirmed endometriosis, if superficial peritoneal lesions are found during future surgery, they can be ablated, but that again is surgeon preference. Ovarian endometriomas should be excised and not drained due to an 80% to 100% recurrence risk.[30,31]

With the combination of a detailed clinical exam and imaging, it is possible to identify most cases of advanced stage endometriosis. When this is suggested by the evaluation in a symptomatic patient, the procedure should be performed by a surgeon experienced in surgical management of these complicated cases. This avoids an incomplete resection followed by referral for repeat surgical procedure. Finally, there is ample evidence that a hormonal regimen should be commenced following surgery in women who do not actively desire fertility.[11,15,19,32,33] A continued partnership with the patient should be fostered, as the typical course is often one of trials of various hormonal formulations over time. Gynecologists are at the forefront of the care for women with endometriosis. An understanding of the evaluation and comprehensive management of the condition therefore is mandatory to improve quality of life for patients. ■

**DISCLOSURES** The author reports no potential conflicts of interest in regard to this article.

**FOR REFERENCES VISIT**
**contemporaryobgyn.net/EndometriosisGeneralist**

# Health risk prediction tool for postmenopausal women

*by* **BEN SCHWARTZ**

Although there are several widely available risk algorithms available for predicting morbidity among older women, a major issue with them is that none are able to assess risk of multiple disease outcomes simultaneously, which greatly limits their clinical practicality. A recent study, published in *Menopause*, describes the development of a web-based calculator that predicts the likelihood of experiencing multiple and competing outcomes over 5, 10, and 15 years.

The study used baseline demographic and medical data from a healthy, racially diverse cohort of postmenopausal women. Participants were ages 50 to 79 at baseline and enrolled in the Women's Health Initiative (WHI) at 40 sites in four regions (South, Northeast, Midwest, and West). The primary outcomes for the analysis included six morbidities plus mortality and were chosen based on their clinical relevance and frequency in the study population (incidence of ~2% or greater at 15 years).

The morbidities for the predictive models were built for (1) myocardial infarction (MI), (2) stroke, (3) lung cancer, (4) breast cancer, (5) colorectal cancer, (6) hip fracture, and (7) death from any cause. The authors used a proportional subdistribution hazards regression model to develop the calculator in a training dataset and used a concordance statistic (C-statistic) to assess model discrimination.

The authors designated the South WHI region as the test data set and women from the other three WHI regions formed the training dataset. The model was built from the training data set while the test dataset was used to measure the validity of the model's performance. They also used a competing risk framework to build the prediction model. The primary approach treats an event besides the primary outcome of interest as a competing event, though the authors note that their definition differs from the classical definition of competing event as one that precludes the event of interest from occurring.

The calculator can be found online at **https://hedlin.shinyapps.io/shiny/**

The study included 161,808 women (119,889 in the training set, 41,919 in the test set). Participants had complete follow-up for 98% of women at 5 years, 78% at 10 years, 45% at 14 years, and 27% at 15 years. The training set was 85% non-Hispanic white, 6% non-Hispanic black, and 9% who reported other race/ethnicities. The test set is 75% non-Hispanic white, 17% non-Hispanic black, 7% Hispanic and 2% who reported other race/ethnicities. Mean age was 63.5 years for the training set and was 62.4 years for the test set.

The authors found the predictive validity of the calculator measured by the C-statistic in the data set for a first event at 5 and 15 years to be: MI 0.77, 0.61, stroke 0.77, 0.72, breast cancer 0.60, 0.59, colorectal cancer 0.67, 0.60, hip fracture 0.79, 0.76, and death 0.74, 0.72. However, they noted that the breast and colorectal cancer predictions yielded slightly higher risk than rates actually observed in the data.

The authors believe that theirs is the first-large scale study to develop a risk-prediction calculator that can analyze multiple outcomes and health risk predictions simultaneously. They believe it represents a significant tool for available treatment planning, health prevention, health maintenance, and patient education. ■

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

**SOURCE**
Hedlin H, Weitlauf J, Crandall CJ, et al. Development of a comprehensive health-risk prediction tool for postmenopausal women. *Menopause*. 2019:1. doi:10.1097/gme.0000000000001411

# Early menopause and risk of CVD

*by* BOB KRONEMYER

An Australian study in *The Lancet Public Health*, which found that women with premature and early menopause were at significantly increased risk of having a non-fatal cardiovascular disease (CVD) event before age 60, has consequential public health and clinical implications.

"The doubling of cardiovascular disease risk in women below the age of 60 years who have premature menopause is concerning and indicates an urgent need to raise awareness of cardiovascular disease risk in younger women," commented two English health professionals not involved in the study: Lizelle Bernhardt, RN, CLAHRC-EM, a PhD student and heart failure specialist nurse in the Department of Cardiovascular Sciences at the University of Leicester in the United Kingdom (UK), and Claire Lawson, PhD, a nurse data scientist at the Diabetes Research Center at the university.

With up to 10% of women experiencing early natural menopause, this population represents a potential target for early and tailored risk stratification.

Bernhardt and Dr. Lawson, whose comments appeared in the same publication, said a common misconception among health professionals and the general public is that cardiovascular disease mostly affects men, at least until older age. The two writers noted that such sex-bias about CVD needs to be confronted, "with emphasis on the increasing risk in younger women, in addition to new sex-specific preventative and therapeutic strategies for reducing and managing cardiovascular disease in women."

Currently, though, sex-specific risk factors are lacking in cardiovascular disease risk algorithms like QRISK and the Framingham Risk Score, which focus on traditional cardiovascular disease risk factors.

The study pooled data from 15 observational studies conducted in five countries and regions (Australia, Scandinavia, USA, Japan and UK) between 1946 and 2013. The primary endpoint was the occurrence of first non-fatal CVD, which was defined as a composite outcome of incident coronary heart disease (CHD) or stroke.

Of the 301,438 women analyzed, 4.3% had a first non-fatal CVD event after menopause – primarily coronary heart disease.

Compared with women who had menopause at age 50 or 51, women under age 40 with premature menopause had the highest risk of CVD: hazard ratio (HR) 1.55; 95% confidence interval (CI): 1.38 to 1.73 ($P < 0.0001$). The study concluded that early menopausal women who smoked, were underweight or obese, and those with lower socioeconomic status were more likely to develop CVD.

"These findings add to previous evidence showing increased influence of some traditional cardiovascular disease risk factors in women compared with men and further emphasizes the need for risk stratification by sex," the comment writers stated. Furthermore, additional research is needed to determine whether the connection between early or premature menopause and the frequency of cardiovascular disease differs by ethnicity.

**WITH UP TO 10% of women experiencing early natural menopause, this population represents a potential target for early and tailored risk stratification.**

Meanwhile, research by the study authors "is timely and underpins the importance of precision medicine across the cardiovascular disease life course," the comment writers noted.

The differences in CVD pathogenesis between men and women stem from both genetic and biological mechanisms, explained the writers, as well as from complex interactions between behavioral and socioeconomic factors. Studies that further illuminate the complex associations between sex and CVD risk are needed to redesign primary and secondary prevention guidelines.

The writers also said there must be a shift away from a one-size-fits-all approach to a more patient-centered strategy to alleviate the increasing global burden of CVD. ■

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

**SOURCE**

Bernhardt L, Lawson CA. Early menopause and risk of cardiovascular disease: an issue for young women. *Lancet Public Health*. 2019. doi:10.1016/s2468-2667(19)30184-7

# Low stress hormones linked to low sexual desire

*by* BOB KRONEMYER

A recent study of women complaining of low or absent sexual desire found their low desire to be linked to hypothalamic-pituitary-adrenal (HPA) axis dysregulation. These women did not have any clinical depression or take any hormonal or pharmacological therapy, were not currently undergoing severe stress and were without health concerns or relationship disharmony considered likely to interfere with sexual desire.

Compared to 138 control participants, 137 women with hypoactive sexual desire disorder (HSDD) had significantly lower cortisol and lower dehydroepiandrosterone (DHEA) levels in the morning, a flatter diurnal cortisol slope and a lower cortisol awakening response (CAR), according to the prospective study in the journal *Psychoneuroendocrinology*.

"We previously found low morning DHEA in 121 women carefully diagnosed with HSDD (without the confounders listed in the first paragraph), but we found similar serum levels of testosterone and androgen metabolites, compared to124 controls," said lead principal co-investigator Rosemary Basson, MD, a clinical professor of psychiatry at the University of British Columbia in Vancouver, Canada.

Those findings suggested that low DHEA is not causative of low desire by being an inadequate testosterone supplier, but potentially reflects HPA axis dysregulation from past stress/neglect/suffering, according to Dr. Basson.

"Research shows childhood stress is connected to HPA axis dysregulation in adult life, therefore, we repeated the study to confirm low DHEA in women with low desire and conduct more extensive testing of HPA dysregulation," Dr. Basson told *Contemporary OB/GYN*.

> Many studies have found lower serum levels of DHEA in women reporting low or absent sexual desire.

In contrast to the extensive research investigating, but not finding an association of women's sexual desire with their testosterone levels, many studies have found lower serum levels of DHEA in women reporting low or absent sexual desire. "Hence confirming low DHEA in our study's carefully assessed women was expected," Dr. Basson said.

Likewise, due to previous research concluding that negative mood may impair sexual desire even when any clinical depression is excluded, "finding low DHEA was not surprising," Dr. Basson said. "DHEA concentrations are known to be particularly high in the brain and to have multiple direct actions, including the modulation of various receptors and synaptic transmissions in the brain, including sigmoid receptors to modulate mood."

The authors suspected their repeated finding of low DHEA reflected HPA axis dysregulation, "given that clinical histories of women with chronic low sexual desire frequently contain details of stressful childhoods and adolescence," Dr. Basson said.

For the current study, when sexual function was measured categorically, HSDD subjects demonstrated significantly lower morning cortisol levels compared to control subjects: 8.20 nmol/L versus 9.36 nmol/L, respectively ($P = 0.02$).

"Research suggests that low basal levels of cortisol and blunted HPA activity might predispose to diseases or disorders, such as mental health problems and possible sexual disorders," Dr. Basson said.

In summary, both hormonal deficiency (DHEA and cortisol) and the past stress that the deficiency is believed to reflect may contribute to low sexual desire. "Lower DHEA may lower mood and possibly act via other

CONTINUED ON PAGE 39

# Global consensus statement on testosterone therapy in women

*by* **BOB KRONEMYER**

For the first time, a global consensus position statement on use of testosterone therapy for women has been published in various medical journals. The statement—which is completed and should be read in its entirety—was prompted because of the uncertain benefits and risks of treating women with testosterone. In many countries, the therapy is prescribed off-label, using either testosterone formulations approved for men with dose modification, or as compounded therapies.

"There is a need to delineate, based on available evidence, when a trial of testosterone therapy is appropriate, to enable women who might benefit to be treated, and equally when it is inappropriate to protect women against inappropriate treatment," said lead author Susan Davis MBBS, FRACP, PhD, FAHMS, president of the International Menopause Society and chair of Women's Health at Monash University in Melbourne, Australia.

Dr. Davis told *Contemporary OB/GYN* that testosterone therapy is effective in women with low sexual desire that causes them distress, as long as their blood levels are within the normal premenopausal range.

"In such women, there is no evidence of serious adverse events," she said. "Few women will experience an increase in hair growth or acne, and when either occurs the effects are mild."

Therapy does not cause alopecia, clitoromegaly or voice change. However, the safety of long-term testosterone therapy has not been determined.

The recommendations are based on findings from blinded placebo/comparator randomized clinical trials (RCTs) of at least 12 weeks' duration of reported outcomes. The authors noted that the diagnosis of hypoactive sexual desire disorder/dysfunction (HSDD) should include a full clinical assessment. Other factors contributing to female sexual dysfunction (FSD) must also be identified and addressed before beginning testosterone therapy. But a blood total testosterone level should not be used to diagnose HSDD.

This statement recommends against using compounded testosterone.

Treatment of HSDD should be limited to testosterone formulations that achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations. Given the absence of any approved female product by a national regulatory body, male formulations can be judiciously used in female doses, but blood testosterone concentrations must be routinely monitored.

The statement recommends against using compounded testosterone. In addition, data are insufficient on which to base a recommendation for use of testosterone in premenopausal women to treat sexual function or any other outcome.

Conversely, testosterone therapy does not increase mammographic breast density nor does short-term transdermal testosterone therapy impact breast cancer risk. However, data from the RCTs are insufficient to gauge long-term breast cancer risk.

But there is strong evidence in the literature that appropriate testosterone treatment benefits sexual function, with an average of one satisfying sexual event per month and increases in the subdomains of sexual desire, arousal, orgasmic function, pleasure and sexual responsiveness, along with a reduction in sexual distress.

The statement also advocates more research on testosterone therapy for women, plus developing and licensing testosterone products indicated specifically for women. The position statement has been endorsed by more than a dozen leading societies, including the International Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, and The International Society for Sexual Medicine. ■

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

## SOURCE

Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the use of Testosterone Therapy for Women. *Maturitas*. 2019;128:89-93. doi:10.1016/j.maturitas.2019.07.001

# STDs on increase in CDC report

*by* JUDITH M. ORVOS, ELS

A new report from the Centers for Disease Control and Prevention shows an alarming rise in incidence of sexual transmitted diseases in the United States. In 2018, combined cases of syphilis, gonorrhea, and chlamydia hit an all-time high and cases of congenital syphilis increased 40%.

***Sexually Transmitted Disease Surveillance 2018* shows that from 2017 to 2018 there were nearly 2.5 million combined cases reported of chlamydia, gonorrhea, and syphilis, and that:**

- Cases of primary and secondary syphilis increased 14% to more than 35,000—the highest number reported since 1991.
- Gonorrhea increased 5% to more than 580,000 cases, also the highest number reported since 1991.
- Chlamydia increased 3% to more than 1.7 million cases, the most ever reported to CDC.

In women, CDC said, syphilis rates increased 30.4% during 2017-2018 and 172.7% during 2014-2018, suggesting a rapidly growing heterosexual epidemic. In 2018, the national rate for congenital syphilis cases was 33.1 per 100,000 births, or a 39.7% increase relative to 2017 and a 185.3% increase relative to 2014. The highest rates of congenital syphilis were reported in 2018 in the west and south, with increases of 49.5% in the south, 44.1% in the northeast, 30.5% in the midwest, and 29.3% in the west during 2017-2018.

In 2018, combined cases of syphilis, gonorrhea, and chlamydia hit an all-time high and **cases of congenital syphilis increased**

**40%**

Also during 2017-2018, the number of syphilitic stillbirths increased, from 64 to 78, as did the number of congenital syphilis-related infant deaths, from 13 to 16. The trends held true in all regions of the country and among all racial/Hispanic ethnicity groups.

Rates of gonorrhea hit a historic low in 2009 but have increased 82.6% since then. During 2017-2018, the overall rate of the disease increased 5.0%, in all regions of the country and among all racial/Hispanic ethnicity groups. From 2014 to 2018, rates of gonorrhea increased 37.2% to 145.8 cases per 100,000.

CDC noted that *Chlamydia trachomatis* is the most common notifiable condition in the United States, with more than 1.7 million cases in 2018, or an increase of 2.9% over 2017. Almost two-thirds of cases of chlamydia reported in 2018 were in individuals aged 15 to 24. Rates of chlamydia increased 1.3% and 0.8% in females aged 15 to 19 and 20 to 24, respectively. The case rate was highest among women in the south, at 744.2 cases per 100,000.

On the positive side, the CDC report indicated that prevalence of human papillomavirus decreased significantly from the pre-vaccine era (2003-2006) to 2011-2014 in women aged 14 to 19 and 20 to 24. ■

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

**SOURCE**

2018 Sexually Transmitted Diseases Surveillance. Centers for Disease Control and Prevention. https://www.cdc.gov/std/stats18/default.htm. Published August 27, 2019.

AGREE? DISAGREE?

Have you seen an increase in these cases in your practice? What is your top STD diagnosis? Email comments to COGEditorial@mmhgroup.com.

# Discussing vulvovaginal health at well woman visits

*by* BOB KRONEMYER

Although nearly half of postmenopausal women reported having vulvovaginal symptoms (VVS), only a minority discussed their symptoms during a well woman visit with a primary care provider or gynecologist, according to a secondary analysis of a 2015 survey of 1,513 postmenopausal women.

"Despite the availability of safe and effective treatments, the Genitourinary Syndrome of Menopause (GSM) commonly affects postmenopausal women and reduces quality of life, yet it is under-recognized and undertreated," said co-investigator Amanda Clark, MD, MCR, NCMP, an affiliate investigator at the Kaiser Permanente Center for Health Research in Portland, Oregon.

Other studies indicate that VVS affects 39% to 51% of women and that 44% to 67% have discussed their symptoms with a health care professional. In addition, "lower urinary tract symptoms affect 75% of women aged 40 or greater, yet less than a third report having sought treatment," said Dr. Clark, who shared survey results at The North American Menopause Society (NAMS) Annual Meeting in Chicago in September.

The survey study was part of a larger intervention trial, to test whether or not an educational initiative for clinicians could improve detection and treatment of GSM. Within 1 to 2 weeks of a well woman visit, women aged 55 and older were invited by email to participate in an online survey about their care experience related to GSM at the visit.

Overall, 45% of respondents (680 of 1,513) reported having VVS. However, only 40% of these women reported discussing the symptoms at the well visit. Well visits for symptomatic women occurred both in primary care (76%) and in gynecology (24%). But when well visits occurred in gynecology, 71% of women reported a discussion about VVS, compared to 30% of women who had a well visit by primary care. Perhaps more disturbing, though, is that it was the patient who was more likely to initiate the discussion than the clinician: 59% versus 22%, respectively.

"As older women stop having annual gynecologic exams related to contraception and reproductive issues, they may be losing access to needed specialty care for genitourinary symptoms that are so prevalent," Dr. Clark told *Contemporary OB/GYN*.

To improve care for GSM, Dr. Clark said there must be increased awareness about GSM among primary care clinicians. "Women may need greater access to gynecology and urogynecology care in their postmenopausal years," she said.

The survey also revealed that when women did have a discussion about VVS with their provider, positive actions were initiated for therapy, including educational handouts, suggestions for over-the-counter (OTC) and prescription therapies, and increased referrals for specialty care.

"Discussions do make a difference," said Dr. Clark, noting that clinicians should ask their patients about VVS symptoms when they present for wellness exam, as women report lack of care-seeking behavior for VVS because they are unaware that symptoms are associated with menopause and unaware that there are safe and effective treatment options.

"GSM is one of the chronic conditions of midlife and older women for which treatment can result in a marked improvement in quality of life, particularly in relieving dryness and pain related to sexual activity," Dr. Clark said.

In addition to OTC lubricants and moisturizers, GSM can be treated with low-dose vaginal estrogen products; intravaginal prasterone (DHEA); and ospemifene, a selective estrogen receptor modulator (SERM). "All of these options have a good safety profile and minimal systemic absorption," Dr. Clark said.

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**Dr. Clark** is a legal consultant for Butler Snow LLC, representing Ethicon, for pelvic mesh litigation.

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

**SOURCE**

Clark AL, Bulkley JE, Bennett AT, Vesco KK. Discussion of Vulvovaginal Health at Postmenopausal Well Woman Visit – Patient Characteristics and Visit Experiences. Presented at: The North American Menopause Society (NAMS) Annual Meeting; September 25-29, 2019; Chicago. https://www.menopause.org/docs/default-source/agm/poster-session-abstracts.pdf.

# Cost-effectiveness of genetic testing in breast cancer patients?

*by* **BEN SCHWARTZ**

While current national and international guidelines recommend genetic testing in women with breast cancer who have relevant family history or clinical criteria, patients with breast cancer and genetic pathogenic variants do not always have a positive family history, potentially leading to improper screening for at-risk women. A recent study in *JAMA Oncology* estimated incremental lifetime effects, costs, and cost-effectiveness of multigene testing of all patients with breast cancer compared with the current practice of genetic testing (*BRCA*) based on family history or clinical criteria.

The microsimulation modeling study compared lifetime costs and effects of high-risk *BRCA1*/*BRCA2*/*PALB2* (multigene) testing of all unselected patients with breast cancer (strategy A) against *BRCA1*/*BRCA2* testing based on family history or clinical criteria (strategy B). Both strategies were evaluated with United Kingdom (UK) and US populations.

Data were collected and analyzed from January 1, 2018 through June 8, 2019. Four large research studies supplied data from 11,836 patients in population-based BC cohorts (regardless of family history). The women in these cohorts were predominantly white and representative of a Western population ethnicity.

For the model, all women with breast cancer underwent *BRCA1*/*BRCA2*/*PALB2* testing in strategy A. In strategy B, only women with breast cancer fulfilling family history or clinical criteria underwent *BRCA* testing. *BRCA*/*PALB2* carriers could undertake contralateral preventive mastectomy, while *BRCA* carriers could also choose to undergo risk-reducing salpingo-oophorectomy (RRSO). Those whose relatives were mutation carriers also underwent cascade testing. Unaffected relative carriers could undergo magnetic resonance imaging or mammographic screening, chemoprevention, or risk-reducing mastectomy for breast cancer risk and RRSO for ovarian cancer risk.

The authors calculated the incremental cost-effectiveness ratio as incremental cost per quality-adjusted life year (QALY) gained. This number was compared with standard £30,000/QALY and $100,000/QALY UK and US thresholds, respectively. All costs in the study were reported at 2016 prices. Incidence of ovarian and breast cancer, excess deaths due to heart disease, and the overall population effects were estimated.

Based on the model results, the authors found that *BRCA1*/*BRCA2*/*PALB2* multigene testing for all breast cancer patients would annually cost £10,464 QALY (payer perspective) or £7,216/QALY (societal perspective) in the UK and $65,661/QALY (payer perspective) or $61,618 QALY (societal perspective) in the United States when compared to current *BRCA* testing based on clinical criteria or family history.

Testing all women with breast cancer was associated with an additional 419-day increase in life expectancy for UK and 298 days for US *BRCA1*/*BRCA2*/*PALB2* pathogenic variant carriers. One year's unselected genetic testing of all patients with breast cancer could prevent an additional 1,142 breast cancer cases and 959 ovarian cancer cases in the UK and 5,478 breast cancer cases and 4,255 ovarian cancer cases in the United States. This finding corresponds to 633 averted deaths due to cancer among UK populations and 2,406 averted deaths among US populations.

The authors found that not only did unselected, high-risk multigene testing for all patients with breast cancer result in significant numbers of averted deaths, but it was also extremely cost-effective compared with testing based on family history or clinical criteria. They suggest that current policy needs to be amended so that genetic testing for all women with breast cancer is the recommended approach. ■

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

# Older women are consuming more alcohol

*by* **BEN SCHWARTZ**

A new study indicates that binge drinking is becoming more prevalent among middle-aged women and clinicians need to do a better job of screening their patients for the condition. The results were presented at the North American Menopause Society annual meeting.

The study indicated that the male-to-female gender gap has been narrowing over the past century and binge-drinking and alcohol use disorder (AUD) are increasing more rapidly among middle-aged and elderly women, minorities, and the socioeconomically disadvantaged. Analysis of face-to-face surveys of approximately 40,000 US adults found that prevalence of any alcohol consumption over 12 months was 73% in 2012-2013, which represented an increase of 11.2% from 2001-2002. Furthermore, prevalence of high-risk drinking (4 or more drinks/day in women) was 12.6% in 2012-2013, representing a 30% increase over the decade.

The greatest change in high-risk drinking, however, occurred in women (58%) and in age groups 45 to 64 and 65 and older. Alcohol-related emergency room visits in the United States were also significantly higher in 2014 compared to 2006: 5.0 million vs 3.1 million, respectively. This increase was largely due to chronic alcohol consumption in women aged 45 to 65.

While the authors note that the reasons for the increase in high-risk drinking are not completely understood, they suggest that the increase could be related to stress from work, stress from retirement, financial pressures, empty nest, or challenges associated with menopause. Further complicating the issue, depression is more common in women than men with AUD, and women are less likely than men to seek treatment for alcohol addiction. The authors also suggest that women can become addicted to alcohol with less exposure over shorter periods of time due to biologic factors because they have reduced gastric alcohol dehydrogenase, causing decreased alcohol first-pass metabolism which leads to higher blood levels of ethanol.

The authors believe these findings indicate a need for better screening of high-risk alcohol use and AUD in women, as well as identification and removal of barriers to treatment. However, more research is necessary to better understand the risk factors involved in excess alcohol consumption among women so that more effective prevention and treatment programs can be developed. ■

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

**SOURCE**

Newman CB. D Alcohol Use in Midlife Women. Presented at: The North American Menopause Society (NAMS) Annual Meeting; September 25-29, 2019; Chicago. https://www.menopause.org/docs/default-source/agm/nams19_invited_regular-lb_abstracts-3_0826.pdf

# Stress hormones, low sexual desire

CONTINUED FROM PAGE *34*

neurotransmission in the brain, due to its many as yet unexplored actions," Dr. Basson said. "So supplementing DHEA could eventually be appropriate. But supplementing DHEA systemically is not yet recommended."

Nonetheless, the study's findings strongly encourage evaluating stress in the younger years of women with sexual low desire. Appropriate cognitive therapies and other treatment modalities for altering response to stress should also be advocated. ■

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

**DISCLOSURE** Dr. Basson reports no potential conflicts of interest with regard to this article.

**SOURCE**

Basson R, O'Loughlin JI, Weinberg J, Young AH, Bodnar T, Brotto LA. Dehydroepiandrosterone and cortisol as markers of HPA axis dysregulation in women with low sexual desire. *Psychoneuroendocrinology*. 2019;104:259-268.

# Decision-support tool improves patient-provider communication

*by* **BOB KRONEMYER**

When counseling a patient who has interacted with the contraceptive decision-support tool *My Birth Control*, providers are more likely to focus on the patient's preferences for contraceptive methods, rather than directive or foreclosed counseling on a specific method. That is the major finding of a prospective study in the journal *Patient Education and Counseling* (PEC), which analyzed 70 audio recordings of counseling visits among 15 providers in four San Francisco safety net clinics.

"There is a need to improve the quality and patient-centeredness of contraceptive counseling, especially given recent trends toward promotion of long-acting reversible contraceptive methods," said principal investigator Christine Dehlendorf, MD, MAS, a professor of family and community medicine at the University of California, San Francisco (UCSF). To address this issue, the investigators developed the digital My Birth Control, which provides women information about their birth control options and prints out their preferences, which in turn can be shared with providers during counseling.

The 72 English-speaking women who participated in the study were ages 15 to 45, not currently pregnant, with a desire to discuss starting or switching a contraceptive method, but not wanting pregnancy within the subsequent 7 months. They were randomized to a preimplementation recording (a recording done before the tool was used in clinic) (n = 31; average age 25) or a postimplementation recording (n = 41; average age 26) with their provider. Both samples were racially and ethnically diverse.

Of the 15 healthcare providers, most were either nurse practitioners (47%) or counselors/ health educators (40%).

Each provider had between one and three audio recordings made of their discussions with patients about contraception before implementation of My Birth Control (an average of two recordings). Similarly, there were one to three recordings after tool implementation (an average of three recordings). A total of 70 recordings were analyzed, after excluding two postimplementation records from one provider, due to lack of discussion about other contraceptive alternatives.

Before tool implementation, eight of 15 providers tended to ask patients if they had a method in mind to use and gave information about that method, without engaging patients about alternative options that might suit them. But after tool implementation, the majority of these discussions of contraception began with a reference to the tool printout.

Differences were also observed in counseling by other providers who had initially used a directive counseling approach, with acknowledgement of patients' stated method preferences as communicated by the tool printout. Even among those providers who had initially used a patient-centered approach focused on patients' preferences, the printout was used as a means to further facilitate this approach.

The experience greatly impacts the patient's ability and willingness to access care in the future and to trust medical advice, according to Dr. Dehlendorf. "Digital tools like My Birth Control have the potential to standardize processes to improve care in a cost-effective and patient-centered manner," she said. ■

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

**DISCLOSURE** Dr. Dehlendorf reports no relevant financial disclosures.

## SOURCE

Holt K, Kimport K, Kuppermann M, Fitzpatrick J, Steinauer J, Dehlendorf C. Patient-provider communication before and after implementation of the contraceptive decision support tool My Birth Control. *Patient Educ Couns*. 2019. doi:10.1016/j.pec.2019.09.003

# Sexual minority women and contraceptive use

*by* BOB KRONEMYER

Complex relationships exist between sexual orientation and contraceptive use among sexual minority women (SMW), according to focus groups and interviews with young adult cisgender SMW. For this study SMW included queer (an umbrella term that contains a variety of sexually diverse identities, including but not limited to lesbian and bisexual), bisexual, lesbian and pansexual women. The findings, which were reported in the *American Journal of Public Health*, showed that compared with their heterosexual peers, SMW have an elevated risk for unintended pregnancy.

Investigators gathered information between August 2017 and April 2018 from participants in three U.S. cities: Chicago; Madison, Wisconsin; and Salt Lake City, Utah. The five focus groups and one-on-one interviews totaled 22 women ages 20 to 30 who identified as queer or non-heterosexual, in addition to being assigned female at birth.

"We wanted to examine contexts in which adult SMW engage in penile-vaginal intercourse (PVI), including norms surrounding contraception within these interactions," said co-principal investigator Jenny Higgins, PhD, an associate professor of both ob/gyn and gender & women's studies at the University of Wisconsin-Madison.

Queer women in the study described a wide range of experiences with contraception. "Many barriers they faced in obtaining and using contraceptives were consistent with those described by straight women: challenging negotiation with partners, contraceptive side effects and dissatisfaction, pregnancy ambivalence, and less frequently cited, healthcare access and insurance hindrances," Dr. Higgins told *Contemporary OB/GYN*.

Study participants also conveyed a variety of contraceptive-related themes that affected queer women in unique ways compared to straight women. For example, the investigators discovered that contraceptive ads and campaigns could exclude queer women from contraceptive messaging. Queer women's resulting lack of self-concept as contraceptive users might impede their ability to prevent unwanted pregnancies. Furthermore, "comparatively less frequent PVI in queer women's lives led to contraceptive nonuse or use of less effective methods when such sex did occur," Dr. Higgins said.

Sexual minority women also face difficulties navigating contraceptive use, due to managing queer identity both within the healthcare system and within their own queer communities. Finally, participants in the study talked about gender-based violence and relationship-based power imbalances.

"We were struck by how commonly the queer women in our study described experiences of sexual coercion and violence in their relationships with cisgender men," Dr. Higgins said. "These encounters could render queer women relatively less able to protect themselves against unwanted pregnancy."

On the other hand, the process of coming out can contribute to sexual empowerment to meet contraceptive needs. "We were surprised by the potential compatibility between contraception and queer identity," Dr. Higgins said. Promoting the noncontraceptive benefits of contraception might also be a way to deliver contraceptive services in queer-friendly ways.

"Providers and practitioners may wish to better underscore these noncontraceptive benefits in their outreach to queer clients and communities," Dr. Higgins said. "Providers can also strive to make contraceptive services, including health histories and contraceptive counseling, more inclusive to queer patients."

Increasing easy, affordable, queer-friendly access to all US Food and Drug Administration–approved contraception may increase contraceptive use as well. "While queer women may face significant barriers in obtaining and using contraception, they also face barriers to becoming pregnant," Dr. Higgins said. "Ob/gyn providers and reproductive health practitioners need to ensure that queer women avoid unwanted pregnancies and achieve wanted ones." ■

**Bob Kronemyer** is a freelance writer for *Contemporary OB/GYN*.

## SOURCE

Higgins JA, Carpenter E, Everett BG, Greene MZ, Haider S, Hendrick CE. Sexual Minority Women and Contraceptive Use: Complex Pathways Between Sexual Orientation and Health Outcomes. *Am J Public Health*. 2019. doi:10.2105/ajph.2019.305211

# Reproductive health care in America

CONTINUED FROM PAGE 10

Subsequently, *Planned Parenthood v Casey* 505 U.S. 833 (1992), was a landmark United States Supreme Court case regarding abortion. This was a first case in abortion history attempting to overturn *Roe v Wade* and came on the heels of the replacement of two liberal judges with two more conservative judges. The case arose from a challenge to five provisions of the Pennsylvania Abortion Control Act of 1982; among them were requirements for a waiting period, spousal notice, and (for minors) parental consent prior to undergoing an abortion procedure. In the opinion, the Court upheld the constitutional right to have an abortion that was established in *Roe v Wade* (1973), but altered the standard for analyzing restrictions on that right, crafting the "undue burden" standard for abortion which permits legislative restrictions to abortion access that do not impose an "undue burden" on women seeking care.

Paralleling the judicial expansion of reproductive rights, in 1970 Congress enacted Title X of the Public Health Service Act. The Title X program established the only federal grant dedicated to providing individuals with comprehensive family planning and related preventive health services, including access to contraceptive services, supplies, and information, with priority given to low-income women. There was bipartisan consensus in the 1960s and early 1970s that access to family planning was a universal human right; the Senate passed the Act with a unanimous vote and only 32 members of the House dissented. For nearly 50 years Title X family planning clinics have played a critical role in ensuring access to a broad range of family planning and related preventive health services for millions of low-income and uninsured individuals.

Title X programs are jeopardized by recent legislative efforts such as the Title X "Gag Rule." The proposed final rule would force a medical provider receiving federal assistance to refuse to promote, refer for, perform or support abortion as a method of family planning. This has led many family planning programs, such as Planned Parenthood, to drop out of participation in Title X rather than attempting to comply with these restrictive regulations. Those who are most vulnerable to the "Gag Rule" are minority women, lower socioeconomic status women, and adolescent girls who are disproportionately impacted by unintended pregnancy rates and subsequent abortion rates, and many rural and urban community health centers, particularly those serving poor women on Medicaid, are left with fewer options for family planning services. The result could be reversal of the 30-year drop in adolescent pregnancy rates and the lower rates of abortion that we have seen over the last quarter century.

Access to affordable and available contraception is the premise of the foundation for Title X and one of the guaranteed preventive women's health services described under the Affordable Care Act. In 2018, ACOG along with at least 10 other health care organizations provided testimony opposing elimination of the contraceptive mandate proposed for Health and Human Services. Worldwide almost 25% of maternal deaths are due to an unmet need for contraception.

## Current legal restrictions

More than a century since the Comstock Act, women's access to reproductive health care including abortion and contraception is threatened through legislative backlash against reproductive choice, and abortion access is more vulnerable than ever due to legislative attempts at the state and national levels to disenfranchise women and marginalize rights to legal reproductive choices. States have enacted a growing number of abortion restrictions that the courts have found not to be "undue burdens," including mandatory waiting periods, physician scripting, parental involvement, and specific facility requirements for abortion clinics. Since *Roe v Wade*, 1200 restrictions have been enacted; recently the pace of abortion restrictions has accelerated, and the nature of the restrictions more severely curtails access. An increasing number of states have passed extremely restrictive abortion laws intending to test the protections of *Roe v Wade* in the Supreme Court.

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# Best financial practices for busy doctors

## Beyond their patients' health, ob/gyns must also take care of their own financial health.

*by* LIS ZIMMERMAN

Doctors are unique. Between clinical and administrative duties, coordinating with other physicians, and keeping up with medical research and advances, you're wearing a lot of hats - so many, that it may become easy to overlook your own financial health. If you don't take care of yourself now, you will pay later.

### Three Main Areas of Practice

Successfully managing your financial health can be broken down into three essential areas of focus. The first is critical care: creating a roadmap to achieve financial security while you work and after you retire. The second is maintaining wellness: this includes regular "check-ups" and adjustments to keep your plan on track. Finally, specialized engagements address lifestyle-related issues that arise as your professional and personal lives evolve.

### Critical Care

Like caring for your patients' physical health, the first step in managing your own financial health is gathering data and creating your roadmap for success. The data you will need includes income, expenses, housing, family, insurance, taxes, investments, and goals, both personal and financial. Over the course of your life, there will be changes, adjustments, and additions to your financial plan, but there are certain pieces that you will want to put in place early. These include:

- **SET UP A SAVINGS PLAN:** As a young investor, one of the most important concepts to understand is the power of compound interest. Saving early is arguably the most important component of your financial plan. First, you'll need to determine how much you should save and how much you are actually able to save. Next, you must decide where you will save, e.g. qualified retirement plan, SEP-IRA, brokerage account, or trust account. Lastly, determine how to allocate those savings according to your financial goals which may include saving for retirement or future college expenses, purchasing a home, or reducing debt.

- **ESTABLISH A BUDGET:** Identify fixed monthly expenses and variable expenses for yourself and your business. Establish emergency funds for unexpected expenses.

- **DEBT:** Be sure to include any school, mortgage, or credit card debt in your budget. Assess whether you can lower your monthly medical school loan payments by consolidating and taking advantage of lower interest rates.

- **EVALUATE RISK: There are multiple types of risks, including:**
  - **MARKET RISK:** This is the delicate balance between taking on enough risk to obtain the growth you need while protecting yourself in the event of a severe market decline. Make sure your savings are invested in alignment with your goals. You will need a mix of stocks and bonds. The stocks will provide the long-term growth and inflation protection, while the bonds will serve as a buffer against market declines. The right mix of stocks and bonds will depend on your personal goals and tolerance for risk.
  - **BUSINESS RISK:** The risk that you will be sued, either personally or professionally, means you could be wiped out financially. Malpractice insurance is an important component of your business insurance, while an umbrella pol-

It's important to review your financial plan regularly—or immediately in the wake of a signficant life event.

icy would add additional liability coverage to your homeowner's insurance in the case of a frivolous lawsuit.

- **PERSONAL CATASTROPHIC RISK:** Ensure that you have adequate life and disability insurance.

## Maintaining wellness: Staying healthy requires regular care

It's important to review your financial plan regularly—or immediately in the wake of a significant life event such as marriage, birth of a child, a health event, death of a family member, divorce, or changes in your practice.

Once each year, review your roadmap, including:

- **INVESTMENT PLANNING:** Make sure your asset allocation is still appropriate given your risk tolerance and goals and rebalance or change your portfolio if necessary.
- **RETIREMENT PLANNING:** The retirement landscape is changing. Americans are living longer, which means they will require a larger pool of assets to support themselves during the 20 or 30 years of retirement. Use a retirement planning tool or meet with your advisor to be sure you are on track.
- **INSURANCE PLANNING:** Review existing coverages and identify any uncovered risks, including health, disability, life, personal liability, business insurance, and long term care insurance.
- **ESTATE PLANNING:** It is critical to have a plan in place so that you have control over how your assets are distributed at your death and who is given authority to make medical and financial decisions on your behalf in the event of your incapacity. By planning ahead, you can also reduce taxes on what you leave behind and minimize the chances of unpleasant and costly family legal battles. Once your plan is developed, it is important to regularly review beneficiaries, trustees, health care representatives, and guardians.
- **TAX PLANNING:** It is important to ensure your tax plan is coordinated with your investment and estate plans.
- **LIFESTYLE PLANNING:** Revisit your goals for your housing, activities, and business including succession planning and multi-generational planning.

## Specialized medicine

As your life and practice evolve, you will encounter issues that call for specific financial actions. Some of the most common topics include:

- **PLANNING FOR YOUR LONG-TERM CARE:** How will you pay for additional care that you or your spouse may need as you age? Will you purchase insurance or self-insure?
- **HOUSING:** Upsizing, downsizing, second homes. Buy or rent? Choosing the right financing for your needs.
- **MULTI-GENERATIONAL FINANCIAL PLANNING:** Work with your parents to make sure they are making adequate plans for their later years. Speak with your children to ensure they are working toward financial independence and intelligence.

## Four key takeaways

Paving a path to financial security requires time and effort—two commodities in short supply for busy physicians. In a study performed by Vanguard, they determined that making smart decisions can add up to 3 percent to a portfolio's return. This could add to the longevity of your portfolio and set you up for long-term success. Starting early is ideal, but it is never too late to begin.

Here is a summary of the most important steps to managing your financial health:

- Begin planning or, at a minimum, saving early. Understand the retirement options that are available to you.
- Cover your risks: business, life, and disability.
- Review your roadmap periodically and after all major life events.
- Coordinate your investment, retirement, tax and estate plans to ensure desired results.

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## When to assume care?

CONTINUED FROM PAGE 49

180 bpm, with absent variability. The FHR then dropped to the 80s and 90s for approximately 7 minutes. The patient was turned to her right and then left side, oxygen was placed, and the FHR gradually returned to the 150s. The patient continued complaining of cramping and back and abdominal pain. The FHR increased to the 170s with minimal variability and no significant decelerations (Category II). The obstetrician recommended a biophysical profile (BPP), which was done and scored at 4 out of 8. "Sluggish movement of the heart" was noted on ultrasound as was an unusual appearance of the fetal small bowel. Radiology recommended a detailed fetal ultrasound if the patient remained pregnant. While in radiology from 10:48 to 11:08 AM, the patient was unmonitored. Upon arriving back on labor and delivery, the FHR was 170 bpm with minimal variability.

The patient was admitted for induction of labor, with a documented indication of an abnormal BPP and suspected placental abruption. On exam, her cervix was 2 cm, with a floating presentation. The obstetrician recommended misoprostol followed by oxytocin. The patient was returned to her family physician for management of induction, which was started at 12:15 PM. At that time the FHR was 160 to 170 bpm, with decreased variability. At 12:45 PM, the FHR revealed an oscillatory pattern between 100 and 140 bpm, with absent variability. The nurses had the patient sign an informed consent for cesarean delivery at 1:00 PM. Shortly thereafter, the FHR returned to a baseline of 160 bpm with minimal to absent variability. This pattern persisted over the course of the next 5 hours, with three spontaneous decelerations to the 70s for 60 to 80 seconds. At 5:50 PM there was an episode of fetal bradycardia to 70 bpm which lasted almost 3 minutes. Although the FHR returned to 130 bpm, there were recurrent late decelerations of 20 bpm, with absent variability. At 6:25 PM, the family physician consulted with the obstetrician, who agreed to proceed with cesarean delivery for non-reassuring fetal status.

> The baby was hypotensive, in shock, and had severe anemia and a glucose of 37%.

The patient was delivered at 7:15 PM, 50 minutes after the decision for cesarean. Apgar scores were 1 and 2 at 1 and 5 minutes, respectively. The family physician provided initial newborn resuscitation as pediatrics had not been called. Deep suctioning revealed bright-red bloody mucous. No umbilical cord gases were obtained. The placenta was not sent to pathology. The operative note did not document presence of an abruption or whether blood was present in the amniotic fluid. Pediatrics arrived approximately 30 minutes after delivery. The baby was hypotensive, in shock, and had severe anemia and a glucose of 37%. Intravenous access was thus difficult. The baby was placed in a hood with 75% oxygen. **Arterial blood gases returned as follows:**

- pH - 7.24
- $pCO_2$ - 48 mmHg
- $pO_2$ - 103 mmHg
- $O_2$ saturation - 100%

The admitting diagnosis in the nursery was severe anemia; hypotension, with severe renal and intestinal compromise; hypoglycemia; probable respiratory distress syndrome; and possible sepsis. The patient was transferred to a university hospital, where the baby was hospitalized for 2 months. The baby had complete renal failure and no renal function, attributed to anoxia at birth, requiring peritoneal dialysis. Diffuse anoxic injury with cerebral infarcts and recurrent seizures also was present. The baby had respiratory distress syndrome, in addition to anemia, thrombocytopenia, hypogammaglobulinemia, thrombocytosis, chyloperitoneum, and peritonitis due to α-hemolytic strep. The baby receives home dialysis for 10 hours per day and is on a transplant list. The baby requires tube feedings and receives growth hormone due to poor growth.

Depositions of the involved physicians revealed only two progress

notes before induction of labor and one with the decision for cesarean delivery, all written by the obstetrician. There were no notes during induction of labor. Further, the obstetrician admitted that he had not assessed the family physician's experience in caring for a pregnant patient who required insulin. In addition, he had no explanation for why he did not assume care of the patient in the labor and delivery unit.

The plaintiff's expert testified that the obstetrician should have assumed antepartum care of the patient when insulin was required for blood glucose control. However, despite this breach, the patient's blood glucose was well-controlled, and the fetus grew appropriately, with no evidence of macrosomia. Further, a detailed ultrasound was indicated with morbid obesity and insulin-requiring diabetes. The expert also testified that induction of labor was contraindicated, due to the non-reassuring fetal assessment and poor Bishop score, with an anticipated extensive time from induction to delivery. Pursuing induction in the presence of significantly abnormal FHR tracings, such as an oscillatory pattern, was a breach of the standard of care. Had the patient been delivered expeditiously after obtaining the abnormal BPP or after the abnormal pattern shortly after induction, the baby would likely have recovered. Further, the obstetrician was negligent in not assuming care of the patient on labor and delivery. Absence of a physician knowledgeable in FHR assessment led to the delay in intervening with a cesarean delivery, directly resulting in the adverse fetal outcome. Compounding the situation was that pediatrics was not called to be at the delivery of the baby.

The obstetrician admitted that he had not assessed the family physician's experience in caring for a pregnant patient who required insulin.

The jury verdict found for the plaintiff, with a verdict of $3.4 million against the physicians, apportioned 80% against the obstetrician and 20% against the family physician.

# COMMENTS

This case presents a unique situation, as areas in the country with limited obstetrical coverage often rely on family physicians to provide obstetrical care. Care can be coordinated between the family physician and the obstetrician. However, it is important to recognize when the care of a patient should either be assumed by the obstetrician, or frequent communication and consultation should occur between the family physician and the specialist obstetrician. This family physician appropriately referred the patient to the obstetrician when the abnormal GTT was obtained. The patient was referred back to the family physician without assessing his experience or comfort level in caring for such a patient. Depositions revealed that the family physician had not personally cared for an insulin-dependent pregnant patient previously. Despite this, the patient's blood glucose levels were relatively well controlled on low-dose insulin, with reassuring fetal antepartum testing. Her blood pressure was fairly well-controlled without therapy.

The patient presented to labor and delivery with symptoms consistent with a placental abruption. Assessment on labor and delivery was not reassuring. The abnormal BPP dictated delivery. However, the patient was a relatively poor candidate for induction of labor, with a non-reassuring FHR tracing, and a long cervix, 2 cm dilated, with a floating presentation (Bishop score = 1). The obstetrician was found to be negligent in not assuming care of the patient at that time. The situation was compounded as the family physician did not document any assessment of the patient for more than 6 hours during the attempted induction of labor. As such, no defense could be constructed for delayed recognition of the abnormal FHR tracings or the delay in proceeding with a cesarean delivery. Although the obstetrician responded to the request for a cesarean delivery in a relatively prompt manner, the lack of his personally managing the patient on labor and delivery could not be justified. ■

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# LEGALLY SPEAKING

*by* JAMES M. SHWAYDER, MD, JD

# When is it time for the ob/gyn to assume care?

Inability to recognize that a patient requires care from a specialist may lead to allegations of negligence.

A 32-year-old G1P0 who lived in a small, remote community presented to her family physician for her first obstetrical appointment at 11w5d. She was noted to have chronic hypertension, with a weight of 254 lb, and a body mass index of 46.45 kg/m$^2$. Her untreated blood pressure (BP) was 130/85 mmHg. She underwent an ultrasound at 17w6d that revealed a single vertex at 17w5d, with an estimated fetal weight (EFW) of 2112 g (41$^{st}$ percentile), with no fetal anomalies visualized. **A 1-hour glucose tolerance test (GTT) at 24w5d showed a glucose level of 191 mg/dL and a 3-hour GTT at 25w3d was abnormal, with the following results:**

- Fasting blood glucose (BG) - 101 mg/dL,
- 1-hour BG - 213 mg/dL,
- 2-hour BG -169 mg/dL, and
- 3-hour BG - 141 mg/dL.

The family physician referred the patient to an obstetrician, who performed a second ultrasound which was consistent with 24w3d, and consistent with the patient dates placing her at 25w5d. The obstetrician recommended placing the patient on insulin and referred her back to the family physician for ongoing care. The family physician observed the patient and did not institute insulin over the next 7 weeks. The patient's blood sugars obtained at various times of the day were reported to be between 110 mg/dL and 240 mg/dL. An ultrasound obtained at 32w4d was consistent with 30w6d. No estimated fetal weight was reported. The patient was referred back to the obstetrician at 33w2d, who again recommended insulin. Further recommendations included fetal testing with weekly non-stress tests (NST) and ultrasounds every 2 weeks. The obstetrician again referred the patient back to the family physician, with a recommendation to institute insulin and induce the patient at 37 to 38 weeks of gestation. Of note, the patient's blood pressure remained relatively stable without treatment.

The family physician instituted lose-dose insulin, at 10 units of regular insulin in the morning. The patient's BG remained between 75 mg/dL (fasting) and 120 mg/dL (post-prandial). The patient had reactive NSTs on a weekly basis. An ultrasound at 34w3d was consistent with 34w0d, with an EFW of 2434 g (32$^{nd}$ percentile), an amniotic fluid index (AFI) of 9.19, and an anterior placenta.

At 8:40 AM at 36w3d, the patient presented to labor and delivery with complaints of cramping, back and abdominal pain, and a small amount of vaginal bleeding. She had a reactive NST with a baseline fetal heart rate (FHR) of 130 to 140 beats per minute (bpm). The obstetrician was consulted, performed a limited ultrasound, and concluded that there was no obvious placental abruption. Approximately 30 minutes after that ultrasound, the FHR revealed an oscillatory pattern between 160 and

FOR MORE LEGALLY SPEAKING TURN TO PAGE 45

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*The majority of patients will test negative, even if they've had sex in the prior 24 hours.*[2]

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**Reference: 1.** Rapid fFN for the Tli$_{iQ}$ System [package insert]. AW-04196, Sunnyvale, CA: Hologic, Inc.; 2017. **2.** McLaren JS, et al. Prediction of spontaneous preterm birth using quantitative fetal fibronectin after recent sexual intercourse. *Am J Obstet Gynecol.* 2015; 212:89e1-5.