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2. The International Healthcare Worker Safety Center (University of Virginia Health System)

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THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our new parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/CervicalCancerCME

Let us know what you think. Email us at COGEditorial@mmhgroup.com
NOW APPROVED

FIRST AND ONLY FDA-APPROVED TREATMENT FOR POSTPARTUM DEPRESSION.¹

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.¹

ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Please see Important Safety Information including Boxed Warning below.¹

To learn more, please visit ZulressoHCP.com

INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness: In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during

Please see Brief Summary of Prescribing Information, including Boxed Warning, on the following pages.
IMPORTANT SAFETY INFORMATION for ZULRESSO (CONT’D)

Excessive Sedation and Sudden Loss of Consciousness (cont’d): interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS): ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the ZULRESSO REMS include:
- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

Suicidal Thoughts and Behaviors: In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

Adverse Reactions: The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Use in Specific Populations
- **Pregnancy:** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm.
  There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZULRESSO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
- **Lactation:** Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.
- **Pediatric Use:** The safety and effectiveness of ZULRESSO in pediatric patients have not been established.
- **Renal Impairment:** No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD).

Controlled Substance: ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

Please also see Full Prescribing Information including Boxed Warning and Medication Guide for ZULRESSO.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ZULRESSO™ (brexanolone) injection (IV), for intravenous use

Rx only

BRIEF SUMMARY OF PRESCRIBING INFORMATION
(For complete details, please see Full Prescribing Information, including Boxed Warning, and Medication Guide.)

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**
- Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.
- Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).
- Because of these risks, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

1 INDICATIONS AND USAGE: ZULRESSO™ is indicated for the treatment of postpartum depression (PPD) in adults.

2 DOSAGE AND ADMINISTRATION
A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion.

Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:
- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Dilution required prior to administration.

3 CONTRAINDICATIONS: None.

4 WARNINGS AND PRECAUTIONS
5.1 Excessive Sedation and Sudden Loss of Consciousness In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients).

Some patients were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and <1 minute of apnea while receiving two times the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour). All patients with loss of or altered state of consciousness recovered with dose interruption.

There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode. During the infusion, monitor patients for sedative effects every 2 hours during planned, non sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation.

After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate.

Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS)

ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Notable requirements of the ZULRESSO REMS include:
- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

5.3 Suicidal Thoughts and Behavior

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

### Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional patients</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer patient</td>
</tr>
</tbody>
</table>

*ZULRESSO is not approved in pediatric patients.

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:
- Excessive Sedation and Sudden Loss of Consciousness.
6.1 Clinical Trials Experience  Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

**Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction**

In the pooled placebo controlled-studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo controlled-studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO treated patients compared to 3% of placebo treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; two patients who had dosage interruption because of loss of consciousness did not resume the infusion.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60 hour treatment period.

**Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=107)</th>
<th>Maximum dosage 60 mcg/kg/hour (n=38)</th>
<th>Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>-</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>-</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>-</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, presyncope, vertigo</td>
<td>7%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>-</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Sedation, somnolence</td>
<td>6%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing, hot flush</td>
<td>-</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 CNS Depressants  Concomitant use of ZULRESSO with CNS depressants (e.g., opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation.

7.2 Antidepressants  In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Pregnancy Exposure**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.

**Risk Summary**

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and ≥3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rabbits at ≥3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively.

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Data**

**Animal Data**

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with fewer live fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Decreased pup viability between postnatal day 0...
and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

8.2 Lactation

Risk Summary
Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as ZULRESSO has low oral bioavailability (~5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data
A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (~10 ng/mL) in ~95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.

8.4 Pediatric Use
The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

8.5 Geriatric Use
PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.

8.6 Hepatic Impairment
Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh ≥7) with no associated change in tolerability.

8.7 Renal Impairment
No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²) or severe (eGFR 15 to 29 mL/minute/1.73 m²) renal impairment.

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m² because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

9.2 Abuse
In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (two times the maximum recommended infusion rate), and 270 mcg/kg (three times the maximum recommended infusion rate) ZULRESSO infusions over a one hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of “drug liking”, “overall drug liking”, “high” and “good drug effects”, the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both doses of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration.

9.3 Dependence
In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation.

10 OVERDOSAGE

Human Experience
There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, two cases of accidental overdosage due to infusion pump malfunction resulted in transient loss of consciousness. Both patients regained consciousness approximately 15 minutes after discontinuation of the infusion without supportive measures. After full resolution of symptoms, both patients subsequently resumed and completed treatment. Overdosage may result in excessive sedation, including loss of consciousness and the potential for accompanying respiratory changes.

Management of Overdose
In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma. Consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION
Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Manufactured for:
Sage Therapeutics, Inc.,
Cambridge, MA 02142 USA

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June 2019
Has gestational hypertension been banished?

Ob/gyns sometimes need to go beyond guidelines when making judgment calls, as is the case with whether to induce at 37 weeks for gestational hypertension.

TABLE 1
Ambivalent delivery recommendations for gestational hypertension

<table>
<thead>
<tr>
<th>Year</th>
<th>ACOG CO 560</th>
<th>ACOG Hypertension Task Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>37 - 38 6/7</td>
<td>37 0/7</td>
</tr>
<tr>
<td>2015</td>
<td>reaffirmed</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>ACOG PB 202</td>
<td></td>
</tr>
</tbody>
</table>

What to recommend for management of women with gestational hypertension since the HYPITAT trial was published in 2009. This trial, performed in the Netherlands, randomized women with gestational hypertension or mild preeclampsia at 36 to 41 weeks' gestation to induction of labor or expectant management. They reported that the women randomized to induction had a significantly lower rate of the maternal composite adverse outcome (i.e., HELLP (hemolysis, elevated liver enzymes, low platelet count), eclampsia, abortion, pulmonary edema, progression to severe disease, thromboembolic disease or major postpartum hemorrhage) (31%) than those in the expectant group (44%). Further, there was no difference in cesarean delivery rates or neonatal outcome. So it seems clearly reasonable to cite this paper as Level A.
evidence for the recommendation that all women with gestational hypertension should be induced at 37 weeks, not 37 completed weeks, but 37 0/7 weeks, which is the same recommendation for women with preeclampsia without severe features. Reasonable, right?

What might give us pause, as noted above, the ACOG experts have struggled with this recommendation over the last 6 years, releasing multiple documents with varying guidelines for delivery timing for women with gestational hypertension (Table 1). In 2013 they even had two different recommendations in the same year. Do not be misled by my questioning of ACOG. I am a strong advocate of ACOG’s work and highly grateful for and respectful of the documents released as guidelines to help ob/gyns provide the best care based on ever-changing data.

Sometimes, however, we have to use our own judgment and look a little deeper. In this example of the ACOG 2019 recommendation that women with either gestational hypertension or preeclampsia without severe features be managed exactly the same, suggesting that these are the same disease, I do take issue.

Let me give you a few important details of the HYPITAT study mentioned above and used as the Level A evidence for this recommendation.

1. The diagnosis of gestational hypertension was diastolic blood pressure (DBP) ≥ 95 mmHg on two occasions, which is not a diagnosis that we use;
2. The only details about monitoring of the expectant group were “...frequent BP measurements, screening of urine for protein with dipstick or PC ratio” and fetal monitoring that was not clarified with regard to frequency;
3. Only 65% of women in both groups had gestational hypertension, the rest had preeclampsia;
4. The mean gestational age at randomization was 38 and a half weeks. So at least half of the patients in both groups were at least 38 weeks at time of delivery (not 37 weeks);
5. Although the maternal composite outcome was significantly less in the induced group, the only adverse outcome that really occurred in the expectant group was development of severe preeclampsia (36% vs. 23%). No woman developed eclampsia, an abortion or died, and there were no differences in neonatal outcome compared to women who were induced;
6. When the women with only gestational hypertension were analyzed, there was no difference in composite outcome between groups (31% vs 38%), while when the women with preeclampsia were analyzed separately, there remained a significant decrease in maternal composite outcome in the women induced compared to those expectantly managed (33% vs. 54%).

There is no doubt in my mind that women who develop gestational hypertension are at high risk of developing preeclampsia and potentially other morbidities associated with preeclampsia.

There is no doubt in my mind that women who develop gestational hypertension are at high risk of developing preeclampsia and potentially other morbidities associated with preeclampsia.
4 hours later and find is 138/90. You rule out preeclampsia. Do you tell her she must be induced? You can tell what I will say: Counsel her, provide excellent instructions for follow-up and a plan for when you would induce her. I say she has gestational hypertension that is not yet preeclampsia. I say this is not the same disease as preeclampsia even if gestational hypertension is on a continuum with a 50% chance of developing preeclampsia. I say ACOG documents are important and useful guidelines, but they are not “the law” (Table 1).4,6,7 I say we are physicians with many years of experience and must use our judgement when making medical recommendations and we must document these discussions and recommendations. What would I do if a woman with gestational hypertension presents at 37 0/7 weeks with a BP of 160/100 and no other sign or symptom of preeclampsia? I would induce. And in between these numbers, what should you do? You know. I hope that we really haven’t banished the diagnosis of gestational hypertension after all these years and that ACOG keeps providing guidelines and we keep using our judgement to provide the best care we can for women. 

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REFERENCES

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SCD and the work of Dr. Doris Wethers

To the Editors:

I read with interest Dr. Andra James’ article about sickle cell disease (SCD). As noted, life expectancy of patients with SCD now approximates 50 years of age, compared to 10 years of age in the 1970s. This major improvement in outcomes didn’t spontaneously happen via genetic mutation or evolution.

It should be known in wider circles that such an improvement in patient outcomes and life expectancy of patients with SCD is primarily due to the yeoman, trailblazing work of Dr. Doris Wethers, a Black female pediatrician who practiced in New York City. I was happy and honored to have had her as my pediatrician when I was a little girl. I used to love to go to her office, smell the rubbing alcohol waft through the air and know that "she helped people feel better." She was instrumental in my becoming a physician.

Dr. Doris Wethers was the third Black female to graduate Yale School of Medicine (1952). She later became Chief of Pediatrics at Knickerbocker Hospital (which previously refused to admit or treat Black patients). She served in that capacity at other hospitals, including Mount Sinai St. Luke’s Hospital in NYC, where in 1958, she became the first Black attending physician.

Wethers opened SCD programs at every hospital in which she practiced and was recognized among her peers and by legislative bodies. Her efforts led to New York being the first state to mandate testing for all children.

As stated in her January 2019 NY Times obituary, Wethers was "renowned for research and advocacy that helped lead to mandatory testing of all newborns for sickle cell anemia."

Because SCD can be found not only in Blacks, in 1987 Dr. Wethers chaired a panel of the National Institutes of Health; "it recommended routine screening of all babies, regardless of race or ethnicity." As a result of Wethers’ work, since 2006, all states now provide universal screening.

I wish to recognize the exemplar work of my former pediatrician, Dr. Doris Wethers.

Melody T. McCloud, M.D.
Founder & Medical Director, Atlanta Women’s Health Care
ATLANTA, GA
Gadolinium-based contrast in breast MRI: What ob/gyns need to know

Concerns have been raised about the safety of GBCA. Experts review the latest data to support counseling of patients who may have repeated exposure.

by ILANA CASS, MD, AND ROLA SAOUAF, MD

Magnetic resonance imaging (MRI) uses magnetic fields to provide detailed anatomic images that reflect distribution and magnetic properties of tissues (specifically of hydrogen nuclei in water and fat) to aid in diagnosis of many pathologic conditions. Gadolinium-based intravenous contrast agents (GBCA) provide additional information based on signal intensity changes after GBCA administration. GBCA are used in approximately 45% of MRI exams in the United States. In the 30 years since the first GBCA was introduced into clinical practice, almost a half billion enhanced MRI studies have been performed worldwide. In the field of gynecology, MRI is widely used to enhance detection of early breast cancers in women at elevated risk, or to better delineate complex pelvic anatomy in the setting of prior pelvic surgery, severe endometriosis, distorting fibroids, cervical, uterine cancer or ovarian cancer.

A recent concern with use of GBCA surfaced in 2014, when the link between permanent high T1 signal in the dentate nucleus and globus pallidus of the brain and repeated prior GBCA exposure was identified. Post-mortem analysis of these deep brain structures confirmed that gadolinium deposition in the brain of patients who had GBCA-enhanced MRI of any part of the body. Specifically, higher signal intensities were seen in patients who had undergone at least six contrast-enhanced MRI examinations compared to patients who had undergone only non-contrast MRI. Case reports in children noted the same pattern of gadolinium deposition as that seen in adult patients following GBCA. Industry-sponsored studies in rats serially exposed to GBCA found progressively higher signal intensity on imaging, which correlated with post-mortem gadolinium concentrations in the brain. Notably, at the time of this writing, no human or animal data have shown any association between GBCA exposure and neurologic toxicity or neurological symptoms related to gadolinium deposition in the dentate nucleus of globus pallidus.

Ob/gyns need to be aware of the current data about gadolinium-based contrast and the potential implications of its use when they order MRI for their patients.

Consensus guidelines on GBCA

In response to the reports of gadolinium deposition in the brain of GBCA-
exposed individuals, the US Food and Drug Administration (FDA) required a new class warning and other safety measures for all GBCA for MRI in December 2017. Updates to GBCA labeling in May 2018 stated that GBCA was safe and should be used when medically necessary, and directed MRI centers to make educational information available to every outpatient the first time they receive GBCA. The FDA Patient Medication Guide includes risk of gadolinium retention associated with the two types of GBCA (linear and macrocyclic) and indicates that linear GBCA appears to result in higher retention for longer periods of time than macrocyclic GBCA. Providers are encouraged to consider patient characteristics that may result in increased risk of gadolinium retention, and to minimize closely spaced or multiple GBCA MRI.

Gulani and colleagues, on behalf of the International Society for Magnetic Resonance in Medicine (ISMRM) summarized the evidence and offered guidelines to clinicians in Lancet Neurology. They highlighted incomplete understanding of the clinical implications and mechanisms that drive gadolinium deposition, and discordant data comparing different types of gadolinium. The authors advised health care professionals to use caution when administering GBCA and to carefully document when and why a specific GBCA is given to a patient. They did not endorse macrocyclic over linear GBCA, and suggested that patient and clinical factors in addition to pharmacokinetics of the available agents should guide selection of the best GBCA. The American College of Radiology independently endorsed the same recommendation. Finally, the ISMRM Summary urged ongoing research to elucidate clinical implications of gadolinium deposition. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has proposed a ban on all linear agents. Radiologists from the National Institutes of Health have recommended that use of macrocyclic rather than linear agents be considered, if possible.

Implications for MRI utilization in gynecology
MRI imaging of the pelvis is indicated to further characterize masses seen on computed tomography (CT) or ultrasound. An MRI without contrast offers sensitivity comparable to CT with contrast and superior specificity in diagnosis of adnexal malignancy following an indeterminate ultrasound. MRI provides better assessment of soft tissue structures and improved localization of pelvic masses, which is useful to discriminate between ovarian and uterine pathology. T2-weighted imaging is helpful in determining whether the lesion is a unilocular cyst, mixed solid and cystic, or homogeneously solid. T1-weighted imaging without and with fat saturation allows for detection of ad-
nexal lesions containing macroscopic fat. Fat-saturated T1-weighted imaging is useful for identifying ovarian endometriomas, extraovarian endometriosis, and other lesions with blood degradation products, such as hemorrhagic cysts. Adding contrast may allow better discrimination between benign and malignant pathology due to the kinetics of contrast enhancement and washout, although its use may vary by institutional MRI protocol.

The incremental additional clinical information that is gained with use of GBCA in MRI evaluation of variant pelvic anatomy and suspected benign pathology is small. Adding GBCA has been shown to improve evaluation of myometrial invasion from endometrial carcinoma and identification of the correct primary tumor when there are multiple sites of biopsy-proven uterine adenocarcinoma. Contrast may also be useful in identifying vulvar cancers and occult inguinal metastases and it has shown to be useful in identifying neoplastic nodules within complex adnexal lesions and distinguishing endometriosis from pelvic inflammatory disease.

Breast cancer screening in high-risk women

Intensive breast cancer surveillance is advised for women at the highest risk of breast cancer. Women with inherited genetic susceptibility due to BRCA and other less well-known germline mutations (CHEK2, ATM, PALB2), family history, prior chest radiation (cumulative dose > 10 Gy before age 30), or calculated lifetime risk of breast cancer exceeding 20% or more are advised to start breast cancer screening between ages 25 and 30. While mammography remains the gold standard for breast cancer screening in the general population, it has been less successful in detection of early, curable cancers in higher-than-average-risk patients. Prospective studies of annual mammography in BRCA-positive women showed an interval cancer rate of 35% to 50% and the majority of invasive cancers were > 1 cm and 20% to 56% of them had lymph node involvement. Some factors cited to explain the poorer detection of BRCA-associated breast cancer may relate to the confounding effect of breast density, which is more common in younger women. Mammography relies upon abnormal tissue density, tissue distortion, and calcifications to identify breast cancers. BRCA1-associated breast cancers tend to be less mammographically detectable than sporadic breast cancers, which has been attributed to their distinctive histologic growth patterns, such as pushing borders, the relative absence of associated ductal carcinoma in situ, and high cellularity.

In observational studies, adding contrast-enhanced MRI to annual mammography in BRCA mutation carriers significantly improved detection of early, treatable breast cancers with a combined sensitivity of 94% compared to 39% with mammography alone. MRI provides a functional assessment of breast tissue. Contrast-enhanced MRI can detect microvascular changes and peritumoral inflammation as the contrast accumulates rapidly, and is then washed out rapidly, in more vascular tumors compared to benign breast tissue. Consequently, annual contrast-based MRI has been incorporated into breast cancer surveillance guidelines for women at the highest risk of breast cancer.

There has been no change to the recommendation of annual breast screening in high-risk women.
MRI CONTRAST

MRI by the American College of Radiology nor the European Congress in Radiology due to the increased benefit of early detection of cancer in these high-risk patients.\textsuperscript{19,25} In view of the concerns raised over GBCA, macrocyclic agents are advised, and alternatives to conventional MRI imaging are being investigated. These include investigations of lower-dose gadolinium scans\textsuperscript{26} or alternative MRI contrast agents such as Feraheme (ferumoxytol an ultrasmall, superparamagnetic iron oxide nanoparticle), which is currently used for vascular imaging.\textsuperscript{27}

Some high-volume centers enriched with populations of BRCA mutation carriers have amended the recommended surveillance for women at high risk of breast cancer. Breast ultrasound may be alternated with annual MRI, in addition to annual mammography. Ongoing study of novel strategies to improve the mammogram, such as use of iodinated contrast and breast tomosynthesis, which creates a 3-D image of the breast by stacking multiple 2D mammographic renderings, are underway in women with BRCA mutations. Such advances may allow reduction in cumulative exposure to GBCA in these high-risk women.\textsuperscript{21}

**Weighing risks and benefits in women at high risk**

While it’s discomforting to consider progressive accumulation of gadolinium in the body over time, the clinical consequences and level of risk associated with GBCA are, as yet, unknown. On the contrary, the consequences of missing an aggressive breast cancer are all too well known. In the absence of an effective non-gadolinium alternative to GBCA, until we have more definitive data on the true risk of gadolinium deposition, we forego surveillance of women at high risk of breast cancer with contrast-enhanced MRI at our peril. Best practice suggests that providers consider the necessity of contrast based upon clinical circumstances, and that macrocyclic rather than linear agents be used when necessary.\textsuperscript{17} Judicious use of gadolinium, coupled with vigilance in identifying women who might be pregnant, can minimize inadvertent fetal exposure to gadolinium, which is estimated to occur in 1 in 860 pregnancies in the United States.\textsuperscript{28}

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

**FOR REFERENCES VISIT** contemporaryobgyn.net/GBCAandMRI
GYNECOLOGY

Vulvar pain, difficulty swallowing, and bleeding with intercourse

What is your diagnosis when vulvar examination shows loss of the labia minora?

by EBONY PARKER-FEATHERSTONE, MD, ROSALYN E. MABEN-FEASTER, MD, DIANA CURRAN, MD, JOHN O. DELANCEY, MD, AND HOPE K. HAEFNER, MD

HISTORY A 56-year-old G2P2 presents with longstanding vulvar pain, difficulty swallowing, and pain and bleeding with intercourse. On vulvar examination, you see loss of the labia minora, fusion of the prepuce over the clitoris, and erosions around the introitus (Figure 1).

WHAT IS THE MOST LIKELY DIAGNOSIS?
A. Lichen planus
B. Lichen sclerosus
C. Vulvovaginal atrophy
D. Vulvar high grade squamous intraepithelial lesion (HSIL)

WHAT OTHER AREAS SHOULD BE EVALUATED?
A. Extra-genital skin
B. Oral and buccal mucosa
C. Vaginal mucosa
D. Esophagus
E. Scalp and nails
F. All of the above

FOR THE DIAGNOSIS, NEXT STEP IN EVALUATION, AND DISCUSSION TURN TO PAGE 18
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Vulvar pain

CONTINUED FROM PAGE 16

**DISCUSSION**

Based on this patient’s history and clinical examination, the most likely diagnosis is lichen planus (LP), a chronic inflammatory condition that can involve the skin, mucosa, scalp and nails. Vulvar LP is a subtype that involves the genital skin with or without involvement of the vagina. Women with vulvar LP may present with one of three subtypes—classic, papulosquamous, or erosive—and often present with complaints of itching, pain with intercourse, vaginal discharge, or bleeding. Some patients may be asymptomatic. The patient in this case represents the erosive subtype of vulvovaginal LP, which is the most common of the three.

**EPIDEMIOLOGY**

LP is uncommon, often presenting in the 5th to 6th decades of life, although it can be seen in younger and older women. The prevalence of LP is not well defined, given limited and often under-reporting of this condition. Current rates for LP in the literature are estimated to be between 0.01% and 3%, although prevalence data specific to vulvar lichen planus are unknown. One study of 37 women with cutaneous LP demonstrated a prevalence of 51% for vulvar involvement.

**ETIOLOGY**

While the exact etiology is not known, LP is defined as a chronic inflammatory condition that can involve the skin, scalp, mucosal surfaces, or nails. It is classified as an autoimmune condition with demonstrated cell-mediated autoimmunity. The proposed mechanism includes T-cell-mediated keratinocyte damage of the basal cell layer of the dermis. LP also is associated with other autoimmune diseases including thyroid disease, alopecia, and vitiligo. Patients with LP should be screened for other autoimmune diseases when clinically indicated. A significant association between hepatitis C and LP has also been reported in the international literature, although the relevance of this in North America is not clear.

**CLINICAL FEATURES**

The clinical features vary based on subtype of vulvar LP. The classic or papular subtype most often presents with pruritus, but can be asymptomatic. On clinical examination you will see flat, papular lesions with a characteristic white, lacy pattern (Wickham’s striae). It is often seen in patients with cutaneous LP of other sites and can sometimes resolve spontaneously. Classic or papular LP does not typically cause scarring. The least common subtype is hypertrophic. Patients will typically complain of pruritus and the appearance is characterized by purple/red brown well-demarcated flat-topped...
shiny papules on keratinized skin. It is most common in the perineal and perianal area and does not involve the vagina. Biopsy is often required, as the plaque-like appearance can mimic other diagnoses. The most common vulvar subtype is erosive, which is seen in Figure 1. Patients will often complain of pain, including dyspareunia, or difficulties with urination. On examination you will see white, lacy papules or red erosions which may involve the vestibule (Figure 1) and vagina (Figure 2).

Erosions can lead to scarring, particularly in the vagina. Architectural changes with loss of tissue can also occur, as seen in Figure 1. Erosive LP can also involve other mucosal surfaces including urethral, oral (Figure 3) and esophageal mucosa. Vulvovaginal-gingival (VVG) syndrome is a specific erosive subtype involving each listed mucosal surface. Sites of involvement may not be concurrent, so history of prior site involvement or symptoms in those sites should be solicited.

**Diagnosis**

Clinical examination is crucial for diagnosis but biopsy may be helpful as well. When performing a biopsy, you should target areas of white reticular borders or erosion. If you are taking a biopsy in the area of an erosion, it is important to biopsy on the border of the erosion, including some normal skin. Tissue should be sent for H&E staining and also for immunofluorescence as often findings can be non-specific on histopathology. Of note, the specimen used for immunofluorescence should be sent fresh. In our clinic, we typically use Zeus Tissue Fixative.

**On H&E staining you will often see the following:**

1. Thickening of the epidermis in a saw-toothed pattern
2. Band-like mononuclear infiltrate in the upper epidermis which hags the dermal-epidermal junction and creates some areas of vacuolar degeneration of the basal cell layer (Figure 4)
3. Individual dyskeratotic keratinocytes within the epidermis
4. Prominence of the granular cell layer
5. Absence of parakeratosis.

**Histopathology**

- Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermoeipidermal junction
- Presence of an inflammatory band that consists predominantly of lymphocytes
- Signs of basal cell layer degeneration, for example, Civatte bodies, abnormal keratinocytes, or basal apoptosis


On immunofluorescence, you will see irregular deposition of fibrinogen, IgM, cytoid bodies and occasionally granular IgG or IgA on staining of the basement membrane.

In 2013, diagnostic criteria for erosive lichen planus were created by electronic-Delphi consensus pooling of members of the International Society for the Study of Vulvovaginal Disease (ISSVD). Nine characteristics were identified with three of nine necessary to confirm the diagnosis (Table 1).
**Treatment**

The goals of treatment are to address symptoms and prevent disease progression. Typically, papular or classic vulvar LP will respond to local treatments such as topical corticosteroids (e.g., triamcinolone 0.1% ointment or clobetasol 0.05% ointment). Hypertrophic vulvar LP can be resistant to topical medications. For erosive vulvar LP, topical corticosteroids such as clobetasol 0.05% ointment and augmented betamethasone ointment 0.05% are the first-line treatments. Intralesional triamcinolone acetonide (10 mg/mL) injections can be helpful for more resistant disease. Typically, 0.1 mL of triamcinolone would treat 1 cm² of tissue. For example, we would use 10 mg for the entire vestibule. However, do not exceed 40 mg for the entire vulva. Injections should be at least 3 to 4 weeks apart and no more than three injections overall. There are some reports on the use of topical tacrolimus 0.1% ointment twice daily for oral and genital erosive lichen planus. In some patients with hypertrophic or erosive vulvar LP, topical therapies are insufficient and systemic therapies are required to meet treatment goals. In these circumstances, we will often partner with our colleagues in dermatology. The most commonly used medications include prednisone (only for flares), methotrexate 5 mg by mouth once weekly or 5 mg subcutaneously once weekly (with folic acid supplementation) building up to 25 mg per week, mycophenolate mofetil 500 mg/day building up to 1.5 g twice daily, and hydroxychloroquine 200 mg twice daily. These medications require monitoring and are titrated up over time to achieve their effects.

For patients with vaginal involvement, we recommend intravaginal hydrocortisone (e.g., hydrocortisone acetate foam 40-80 mg nightly, or 25 to 200 mg suppository or cream nightly). For higher doses a compounding pharmacy is necessary. The patient should also dilate daily to keep the vagina open.

Despite these therapies, there are some cases in which vulvar and/or vaginal agglutination occurs despite conservative therapy (Figure 5). At the University of Michigan Center for Vulvar Diseases, we have developed and utilized a protocol to address this population of patients. Our protocol entails a combination of sharp dissection with blunt pressure with an end-to-end anastomosis sizer placed rectally to help define the plane between the vagina and the rectum. Once normal length and width are achieved, a foam dilator covered with two sterile condoms is placed in the vagina and secured via suturing the labia majora together. A Foley catheter is placed prior to this. The patient presents to clinic for removal of the dilator and Foley catheter 48 hours after surgery and then is started on a protocol of daily dilator therapy followed by high-dose intravaginal steroids. Refer to the referenced article for a video and also postoperative recommendations.

Data from a small series at our center (11 women) have shown that 95% of patients were satisfied with their postsurgical result with 55% engaging in intercourse following surgery and 75% with improvement in voiding symptoms.

If a patient is noted to have extensive extra-genital involvement, it is important to collaborate with other specialists such as dermatology and gastroenterology for comprehensive treatment.

**Long-term management**

Surveillance is key as there is an increased risk of squamous cell carcinoma in cases of LP. At the Center for Vulvar Diseases at Michigan Medicine, we follow patients with LP every 6 months by clinical exam. We also recommend patients be up to date on lower genital tract cancer screening. Because the condition can also have a significant impact on quality of life due to pain and issues with sexual functioning, our clinic takes a comprehensive approach with sexual health counselors on site. If this is not available in your clinic, consider referral to sexual health counselors, psychologists, and psychiatrists to help manage these complex patients.

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

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* Actual patient comment from anonymous survey

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Substance use in the breastfeeding woman

Substance use need not be an absolute barrier to breastfeeding, but drug- and patient-specific guidance with counseling free of bias are the keys.

by MARGUERITE LISA BARTHOLOMEW, MD, AND MEN-JEAN LEE, MD

According to the 2016 National Survey on Drug Use and Health, one in 10 people (28 million) over age 12 used an illicit drug in the past 30 days. For young adults aged 18 to 25, use ranges as high one in four for illicit drug use, one in 10 for heavy alcohol use, and two in five for binge alcohol use. Use is primarily driven by marijuana and misuse of opioid pain relievers. Of pregnant women, 6.3% used illicit drugs, 8.3% reported alcohol use, and 4.3% reported binge drinking in the last month.1

Breastfeeding is a major public health strategy because of the well-known benefits, including child spacing, and reduced rates of sudden infant death syndrome (SIDS), childhood infections, and postpartum depression. These benefits may be particularly important for families struggling with substance use. Both the American Academy of Pediatrics (ACP) and the World Health Organization (WHO) recommend exclusive feeding with breastmilk during the first 6 months of life.2,3 The Healthy People 2020 targets are 81.9% for ever breastfeeding and 60.5% for any breastfeeding in 6 months.4 In 2010, The Patient Protection and Affordable Care Act and Fair Labor Standards Act mandated that working mothers be given reasonable break time and a private place to pump that is not a bathroom for up to 1 year after childbirth.5 A woman with substance use (SU) or substance use disorder (SUD) has the same rights and desires as any other mother to receive unbiased counseling and make an informed decision about breastfeeding and is not immune to the medical and societal pressure that “breast is best,” as noted in official statements from organizations regarding breastfeeding and substance use (Table 1).

Screening for drug use

The American Academy of Pediatrics, American College of Obstetricians and Gynecologists (ACOG), and the American Society for Addiction Medicine (ASAM) recommend that all pregnant women be screened for drug use by using a validated screening questionnaire and intervention techniques to counsel abstinence and refer for treatment those who meet criteria for a SUD.6 Further, ACOG states that routine laboratory testing of biologic samples is not required.8 The validated screening questionnaires are linked with education and intervention strategies, and are superior to urine drug screen-
ing (UDS) to detect use. If a UDS is used, it requires informed consent and should be ordered as a preliminary test with a reflex confirmatory test. Using UDSs to triage breastfeeding has limitations and potential to stigmatize and drive women away from medical care. Substances stay in maternal urine and breastmilk for different lengths of time, assays vary, medications can cross-react, use of reflex confirmatory tests may be inconsistent, false-positives and -negatives can occur, and there may be an arbitrary potentially biased focus on certain drugs and which mothers to test. A negative UDS test does not preclude use, nor does a positive test guarantee that the breastmilk contains harmful levels of a drug.

Hospital protocols vary widely in how hospitalized newborns are triaged to receive their mother’s breastmilk. Some rely on biological testing of urine or milk at delivery. Others do not use biological testing, do not initially withhold breastmilk, and provide education and supportive intervention first before deciding about ongoing breastfeeding recommendations. The latter better supports the ethical framework put forth by ACOG to discourage breastfeeding exclusion and separation of parents from their children solely based on suspected or confirmed SUD.

**Consequences of biologic screening for drug use**

Providers have an obligation to be aware that there are potentially serious legal and social consequences of detecting illicit substances in pregnant and lactating women. After the 2010 Child Abuse and Prevention and Treatment Act passed, all states developed policies for health care providers mandating reporting of newborns and other children (not fetuses in federal law) who are exposed to illicit substances under the definition of child abuse or neglect. In 23 states plus the District of Columbia, laws designate substance use during pregnancy to be child abuse. Some states are criminally prosecuting pregnant women for SU during pregnancy. Federal regulation 42 CFR Part 2 protects the privacy of addiction treatment records, however, state laws supersede this protection. Pregnant women should provide written informed consent for UDS and receive no punitive action for refusal. Criminalizing pregnant women for substance use is unethical, counter-intuitive to the physician-patient therapeutic alliance, and does not provide a compassionate solution for the care of motherless children. The American Academy of Addiction Medicine and Amnesty International oppose policies that criminalize substance use by pregnant women.

**Breastfeeding rates in women with SUD**

Rates of breastfeeding are lower in women with SUD. A 2011 study noted that 14% of mothers who used illicit substances or were on opioid maintenance...
therapy breastfed vs. 50% in the general population. In another 2019 study, the prevalence of breastfeeding was high for those receiving prenatal medication-assisted treatment. Prenatal intention to breastfeed was 87% for buprenorphine and 81% for methadone-treated mothers \( (P = 0.25) \). Exclusive breastfeeding at hospital discharge was 31% for buprenorphine and 19.6% for methadone-treated mothers \( (P = 0.06) \). The perception of breastfeeding “contraindications” is important to mothers with SUD. In a 2003 cohort of 393 low-income inner-city women, 48% never initiated breastfeeding and 16% had a documented contraindication to breastfeeding. Of those who never initiated breastfeeding, 42% with a contraindication to breastfeeding cited “not wanting to pass dangerous things” as the reason for not breastfeeding. Of those with contraindications, 75% used cocaine, 28% had HIV infection, 5% used PCP, and 3% heroin or methadone.14

### How ob/gyns can help
Lactation is a bodily function that cannot ethically be regulated or banned by a medical or government authority. Unless a child is removed from the mother, she will have the ability to provide breastmilk to her child regardless of her lifestyle choices. It is more consistent with a therapeutic alliance, autonomy, and beneficence to counsel women that use of certain drugs is not recommended while breastfeeding (and why) instead of the inverse, “You cannot breastfeed if you have used drugs.” Recommendations should be based on an evaluation of the desire for SUD treatment and be free from intrinsic or organizational biases. Alternate nutrition should be considered with maternal permission when SUD treatment and/or mental health stability are in significant jeopardy.

Women with SUD may have fewer role models, lower self-esteem, and may make the assumption that successful breastfeeding is not achievable. A history of abuse may make it difficult. Breastfeeding may trigger flashbacks or shame, making trauma-informed counseling important. Information provided in a self-esteem-building manner about the potential harms of particular substances in the breastmilk may be enough to motivate a woman to stop using substances or practice responsible harm reduction while breastfeeding. Women with chronic drug use resulting in brain dysregulation may find breastfeeding overwhelming or impossible. Maternal behavior may become disrupted where stress becomes heightened by neonate behavior instead of what would normally be rewarding to mothers who do not have a SUD. As a result breastfeeding may be more harmful than helpful. The ideal situation for successful breastfeeding is for a mother to be abstinent from substance use, part of a comprehensive substance use treatment program (ideally gender specific), and if indicated, stable on medication-assisted treatment. If abstinence is not possible, but harm reduction strategies are reliably
implemented, the benefits of breastfeeding can outweigh the risks. Harm reduction strategies include compliance with provider visits and, as needed, pumping and discarding milk, feeding with donor milk or formula, seeking an alternative childcare provider, and avoidance of co-sleeping with the baby when using drugs.

For breastfeeding success, the provider approach and environment should be optimized. It is critical to treat SUD as a chronic relapsing disease, work to avoid mixed messages, and avoid pejorative language like “junkie,” “drug seeker,” and “addicted baby.” Assess the mother’s comfort level and exposure of breast and body. Ask permission before examination, respect boundaries, provide a breast pump and lactation consultation familiar with mother-infant SUD, and avoid encouraging discontinuation at the first sign of difficulty. Regardless of breastfeeding success, the mother’s progress in recovery is most important for the infant’s health and development.4,13 Table 2 summarizes how ob/gyns can help facilitate breastfeeding women with SU and SUD. Table 3 summarizes recommendations for specific substances and breastfeeding.17,18

**Impact of specific substances on breastfeeding**

**Methadone**
The concentration of methadone in human milk is low and women on methadone maintenance should be encouraged to breastfeed regardless of methadone dose.19,20 Neonatal abstinence syndrome (NAS) occurs in approximately 70% of neonates born to mothers prescribed methadone and may negatively influence latch and sucking. Because NAS is significantly reduced in neonates whose mothers breastfeed while on methadone maintenance,21 vigorous efforts to encourage and support mothers to breastfeed are needed. Once NAS is resolved, strategies to reduce long-term exposure to the neonate include feeding or pumping before daily dose and or waiting 2 to 4 hours after a dose.

**Buprenorphine**
Buprenorphine is a partial opioid agonist with few side effects and has be-
come a successful therapy for medical-assisted treatment of opioid SUD. Levels of buprenorphine are low in human milk and are not likely to cause negative effects in the infant. Breastfed infants whose mothers used buprenorphine have less severe NAS and have excellent rates of breastfeeding (76% breastfed at all and 66% were breastfeeding at 6 weeks post-delivery), as is the case with methadone. Breastfeeding is encouraged for mothers using buprenorphine.

**Other prescription opioids**
Short courses of low-dose prescription opiates other than codeine can be used safely during breastfeeding. Codeine use during breastfeeding is discouraged by the US Food and Drug Administration because its metabolite is morphine and some infants may be ultra-rapid metabolizers (URM; carriers of more than two copies of the gene CYP2D6). URM create high blood levels of morphine, which can lead to respiratory arrest. URM occurs in about 2% of the population, but is more common in particular ethnic groups (28% in North Africans, 10% in Caucasians, 3% in African Americans). There is little information available on the safety of breastfeeding when moderate to high doses of opiates are used for long periods of time. Opioids with minimal secretion into breastmilk such as hydrocodone are preferred. Infants younger than age 1 month who are being exclusively breastfed by mothers using opiates in high doses or long term should be observed for any signs of excessive somnolence or sedation.

**Heroin**
Heroin (diacetylmorphine) is metabolized into morphine, which has an elimination half-life of 2 to 3 hours. At therapeutic doses, most opioids like morphine are excreted in breastmilk in minimal amounts. Heroin has an elimination half-life of 15 to 30 minutes, is rapidly excreted into breastmilk, and causes dependence in the infant, however, milk plasma ratios are not well known. Breastmilk should be pumped and discarded for 24 to 48 hours after use which may be impractical. Mothers using heroin who cannot enter treatment or manage harm reduction strategies should be counseled not to breastfeed.

**Cocaine**
High concentrations of cocaine are found in breastmilk screening in recent years.
Urologic chronic pelvic pain syndrome (UCPPS) has a significant negative effect on female sexual function, particularly for lubrication and pain. A systematic review and meta-analysis in the *International Urogynecology Journal* also found that patients with UCPPS were at much higher risk of dyspareunia and that psychosocial variables might be a factor in pathogenesis of female sexual dysfunction (FSD).

The authors searched PubMed, EMBASE, the Cochrane Library and Google Scholar for published literature about the Female Sexual Function Index (FSFI) or reporting the prevalence of dyspareunia. Nine case-control studies, mostly single-center studies, which enrolled a total of 4,965 subjects, were analyzed. All studies were published in English between 2001 and 2014, with sample sizes ranging from 86 to 1,781. Five studies originated from North America and the other four from Europe, with four studies assessing the six individual FSFI domains and five studies evaluating dyspareunia.

Mean age of the case and control groups ranged from 34.8 to 50.6 and from 36.1 to 50.66 years, respectively. Overall quality of the studies was considered moderate to good, with an average Newcastle-Ottawa Scale (NOS) score of 6.5 for risk of bias.

The analysis found a strong correlation between UCPPS and dyspareunia (odds ratio [OR] = 11.27; 95% confidence intervals [CI]: 5.15 to 24.67) \((P < 0.00001)\). The UCPPS group also had significantly lower scores for each of the six individual domains of the FSFI compared with the healthy control group: desire (mean difference [MD] = -1.04; 95% CI: -1.20 to -0.88 \((P < 0.00001)\); arousal (MD = -1.78; 95% CI: -2.36 to -1.20 \((P < 0.00001)\); lubrication (MD = -2.11; 95% CI: -2.49 to -1.73) \((P < 0.00001)\); orgasm (MD = -1.50; 95% CI: -1.72 to -1.28) \((P < 0.00001)\); satisfaction (MD = -1.54; 95% CI: -1.97 to -1.12) \((P < 0.00001)\); and pain (MD = -2.89; 95% CI: -3.63 to -2.14) \((P < 0.00001)\).

Moreover, the FSFI total score was significantly lower for the UCPPS group (mean difference [MD] = -11.35; 95% CI: -14.54 to -8.16) \((P < 0.00001)\).

The pathogenic mechanism of FSD may involve aging, reduced estrogen levels and psychosocial variables, according to the review authors. “Pain may also lead to pessimistic, fearful, and disappointing sexual psychologic disorders, and patients may appear to avoid or reduce the frequency of sex, loathe sexual activity, and further reduce sexual dysfunction,” the authors wrote.

In fact, the main cause of UCPPS in the majority of patients with sexual dysfunction might be psychologic factors, thus forming a vicious cycle of “painful discomfort-psychologic symptoms-sexual dysfunction.”

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network advocates an interdisciplinary strategy to diagnose and treat, which is more effective than monotherapy. However, to break this cycle, more valid therapies and treatments are needed, according to the review authors.

One drawback of the review is that the pooled analysis was limited to the FSFI total score, scores of six domains and prevalence of dyspareunia. In addition, there were no standard criteria for evaluating the scale and diagnosis of FSD, nor was the frequency of FSD fully explained.

“Future well-designed research is called for to develop a comprehensive estimate of the association between UCPPS and FSD,” the authors concluded.

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

**SOURCE**
For noninvasive detection of rectosigmoid endometriosis, magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVS) provide comparable high accuracy and positive post-test probabilities, according to a systematic review and meta-analysis in the journal PLOS One.

Although both modalities are employed for noninvasive diagnosis and preoperative mapping of rectosigmoid endometriosis, there remains no consensus as to which method is the most accurate.

The Brazilian review authors culled MEDLINE, Embase and Latin American and Caribbean Health Science Literature (LILACS) electronic databases to identify studies published in Portuguese, English, Spanish or French through February 2019. The eight studies analyzed comprised a total of 1,132 women who underwent both TVS and MRI for suspected endometriosis, based on clinical history (pelvic pain or infertility) and/or physical examination (pain and nodulation on palpation). The quality of the studies was considered good overall, with seven studies classified as being high-quality and one study of moderate quality.

Pooled sensitivity, specificity, positive likelihood ratios and negative likelihood ratios for MRI were 90% (95% CI: 87% to 92%), 96% (95% CI: 94% to 97%), 17.26 (95% CI: 3.57 to 83.50) and 0.15 (95% CI: 0.10 to 0.23), respectively. The values for TVS were 90% (95% CI: 87 to 92%), 96% (95% CI: 94% to 97%), 20.66 (95% CI: 8.71 to 49.00) and 0.12 (95% CI: 0.08 to 0.20), respectively. In addition, areas under the S-ROC curves (AUC) showed no statistically significant differences between MRI (AUC = 0.948) and TVS (AUC = 0.930) in diagnosis of rectosigmoid endometriosis ($P = 0.13$).

The average prevalence of rectosigmoid endometriosis among the studies was 47.3% (ranging from 16.4% to 76%), for which both methods demonstrated similarly high positive post-test probabilities: 94.8% for MRI and 93.9% for TVS. Combined use of MRI and TVS yielded an even higher post-test probability: 99.6%.

“Noninvasive diagnosis is important, as patients with this condition may go through numerous consultations and examinations, with the time from symptom onset to final diagnosis extending up to 7 years,” the authors wrote. However, the interval between TVS and MRI examinations was not reported in any of the eight studies and the interval between the TVS/MRI and reference standard examinations was not reported in three studies; thus these omissions may have caused some bias.

The authors noted that there is increasing interest in noninvasive diagnosis of deep endometriosis via laboratory tests (serological markers) or imaging examinations. Also, over the past decades, TVS and MRI have demonstrated more accuracy than other imaging methods like transrectal sonography, barium enema, and computed tomography colonography for detecting rectosigmoid endometriosis. TVS and MRI are also less invasive and do not require sedation.

“The study findings suggest that the combined use of TVS and MRI is reasonable, as the chance of noninvasively and accurately diagnosing rectosigmoid endometriosis rises to practically 100% when both examinations yield positive results,” the authors wrote.

Despite the review’s encouraging findings, there was a lack of bowel preparation, which increases the accuracy of intestinal lesion detection. None of the included studies had this procedure for both TVS and MRI. “Both examinations can be performed on the same day, requiring a single bowel preparation, which we believe is important to increase the detection rate of small lesions,” the authors wrote.

A second limitation of the analysis is that only the rectosigmoid colon was investigated in all the studies, therefore preventing the scope of the meta-analysis from encompassing other intestinal locations beyond the rectosigmoid. No study compared lesion characteristics either, which greatly influences surgical planning.

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

SOURCE
Age at menopause and type 2 diabetes mellitus (T2DM) has long been a controversial topic in the field of endocrinology. A recent systematic review and dose-response meta-analysis of six cohort studies has shed light on this issue.

The meta-analysis, published in the journal *Primary Care Diabetes*, included a total of 267,284 women and 19,654 cases of T2DM. The group with the latest age at menopause had a 36% lower risk of T2DM (95% confidence interval [CI]: 0.44 to 0.94) as compared with those who had the earliest menopause. Risk of T2DM was reduced by 10% (RR 0.90; 95% CI: 0.84 to 0.98) with each 5-year increment in age at menopause.

“Age at menopause is associated with a lower risk of type 2 diabetes mellitus (T2DM), according to a systematic review and dose-response meta-analysis of six cohort studies. Although early menopause has previously been linked to an increased risk of T2DM, the quantitative association between age at menopause and T2DM has been unclear, according to the Chinese review authors. The meta-analysis in the journal *Primary Care Diabetes* consisted of studies from the PubMed, Embase and Web of Science databases through January 5, 2019, totalling 267,284 women and 19,654 cases of T2DM. Four studies were from Europe. The group with the latest age at menopause had a 36% lower risk of T2DM (95% confidence interval [CI]: 0.44 to 0.94) as compared with those who had the earliest menopause. Risk of T2DM was reduced by 10% (RR 0.90; 95% CI: 0.84 to 0.98) with each 5-year increment in age at menopause.

“We found an inverse linear association between age at menopause and T2DM.”

The authors noted there has been debate about the connection between age at menopause and T2DM, and that epidemiological evidence remains inconsistent.

“Associations between age at menopause and risk of T2DM are usually attributed to the function of the reproductive system and changes in levels of hormones, including endogenous estrogen and androgen,” they wrote.

A mouse study published in 1980 found a decline in ovarian function that was linked to impaired pancreatic beta-cell function, which is closely associated with glucose metabolism and risk of diabetes.

In addition, both the Heart Estrogen Progesterin Replacement Study (HERS) and the Women’s Health Initiative (WHI) concluded that estrogen therapy could significantly lower the prevalence of diabetes. A separate study indicates that estrogen plays a vital role in preventing diabetic peripheral vascular disease.

Also posing significant risk for diabetes are lipid metabolism, body composition, body mass index (BMI) and fat mass, all of which change rapidly in postmenopausal women. However, controlling the occurrence of diabetes is possible, as age at menopause is influenced by cigarette smoking, education level, and BMI.

Despite its many strengths, the meta-analysis is limited by inclusion of only six studies, all of them observational, for which the demonstrated intensity of causality is low. Furthermore, age at menopause was gleaned by self-reporting or interview, thus subject to recall error. The women in the included studies also had either natural, surgical or medical menopause. The review authors did not assess the effects of surgical or medical menopause on age at menopause and T2DM.

Two studies were of women with only natural menopause, one study of women with natural or surgical menopause, and the remaining studies did not mention the type of menopause.

Nonetheless, “the subgroup analysis by type of menopause and sensitivity analysis showed that the results of our meta-analysis were stable and have reference value for the target population to some extent,” the authors wrote.

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

**SOURCE**


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**Cardiovascular disease and risk of early menopause** New research examines whether women who experience a heart attack, stroke or other type of cardiovascular event before age 35 have a higher risk of early menopause.

*contemporaryobgyn.net/CVDmenopause*
OBSTETRICS

Does drug treatment work for obstetric cholestasis?

by JUDITH M. ORVOS, ELS

Ursodeoxycholic acid is a common treatment for hepatobiliary disorders and it has been used to treat pregnant women with intrahepatic cholestasis. Results of a new study by investigators in UK call into question the wisdom of that approach in obstetrics.

Published in The Lancet, the findings are from a double-blind, multicenter, randomized, placebo-controlled trial conducted at 33 hospital maternity units in England and Wales. Women aged 18 or older at 20 to 40 weeks, 6 days gestation with a singleton or twin pregnancy, and no known lethal fetal anomaly who had intrahepatic cholestasis were recruited. Diagnostic criteria for the liver disorder were based on guidelines from the Royal College of Obstetricians and Gynaecologists and all women had increased bile acid concentrations.

Randomization was to ursodeoxycholic acid or placebo, given as two oral tablets daily at an equivalent dose of 500 mg twice a day. At the clinician’s discretion, the dosage could be adjusted, to a maximum of four tablets and a minimum of one tablet daily. A recommendation was made to the clinicians to continue the treatment from enrollment until delivery. In both groups, two-thirds of participants took a maximum of one tablet twice daily.

The primary outcome was a composite of perinatal death (in utero fetal death after randomization or known neonatal death up to 7 days after delivery), preterm delivery (<37 weeks’ gestation), or neonatal unit admission for at least 4 hours. Secondary maternal outcomes were maternal serum concentrations of bile acids, alanine transaminase (or aspartate transaminase), total bilirubin, γ-glutamyl transferase, and maternal itch score.

Six hundred and five women were included in the study, with 304 women and 322 infants in the treatment group and 300 women and 318 infants in the placebo group. There was no difference in the neonatal primary composite outcome occurring in 23% of the infants in the treatment group, versus 27% of the infants in the placebo group.

Looking at maternal outcomes, the maternal itch scores were significantly lower in the women in the treatment group than in the placebo group. The maternal itch scores were significantly lower in the women in the treatment group than in the placebo group.

Although the authors concluded that “although ursodeoxycholic acid appeared to be safe, it had no clinically meaningful effect on maternal itch symptoms”, the itch symptoms did significantly drop in the women treated with ursodeoxycholic acid. It is not clear how the authors determined this was not clinically significant and for women with cholestasis of pregnancy, itching is their main complaint.

They noted that because their study included women with pruritus and abnormal bile acid concentrations, the results reflected “real-world” effectiveness of the intervention.

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

SOURCE

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Results of a Phase III study suggest that a microbiidal vaginal gel may hold promise for prevention of recurrent bacterial vaginosis (BV). The findings were presented at the 46th Annual Meeting of the Infectious Diseases Society for Obstetrics and Gynecology (IDSOG), held in Big Sky, Montana from August 8 to 10, 2019.

Led by researchers from the University of Alabama at Birmingham, the study was a randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of astodrimer gel. The gel is a microbicide containing astodrimer sodium that is applied topically to the vagina, which has also been studied for prevention of HIV.

For this study, 864 women aged 18 to 45 were enrolled at 67 centers in the United States, Canada, Mexico, and Puerto Rico. All had a history of recurrent BV over the past year and a current diagnosis of BV, based on 3 of 4 Amsel criteria and a Nugent score (NS) of 4. They received 500 mg of metronidazole orally twice daily for 7 days and then were randomized to either 5 g of astodrimer 1% gel or placebo, given vaginally every other day. The women were evaluated for BV ev-ery 4 weeks and after 16 weeks, those who had no recurrence of BV were followed for up to 12 weeks after termination of therapy.

Recurrence of BV—defined as 3 Amsel criteria at or by Week 16—was the primary endpoint. The investigators also assessed time to recurrence, recurrence of symptoms, individual Amsel criteria, and NS 7 to 10.

The astodrimer sodium gel was associated with a lower rate of recurrence than placebo—44.2% vs. 54.3% ($P = 0.15$) and in the women treated with it, time to recurrence was significantly longer ($P = .007$). It was also associated with significantly less frequent recurrence of vaginal odor and/or discharge at or by Week 16 (27.9% vs. 40.6%; $P = .002$) and with the exception of pH, the rate of recurrence of Amsel criteria was lower in the women who used the gel. Using a composite of NS 7-10 and Amsel criteria to define BV recurrence, the authors also found that the rate was significantly lower in the treatment group.

Adverse events were similar in the women using the gel and those using placebo (12.2% vs. 11%). Candidiasis occurred in 14.6% of the group given gel vs. 8.9% of those given placebo during treatment, falling to 4.1% and 5.8%, respectively, during the follow-up period.

"Astodrimer gel has potential as a safe and effective, novel, non-antibiotic therapy for reducing recurrent BV," said the authors while noting the low rates of candidiasis, which they called a "very common" side effect of antibiotics.

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

SOURCE
CONTRACEPTION

Immediate postpartum LARC for women at high risk for medical complications

SUMMARY OF SMFM CONSULT SERIES #48

by THE SOCIETY FOR MATERNAL–FETAL MEDICINE (SMFM) PUBLICATIONS COMMITTEE

Introduction
Reproductive planning is essential for all women and most important for those with complex health conditions or at high risk for complications. Medically complex women are at increased risk for unintended pregnancy compared to a healthy cohort, and for these women, an unintended pregnancy in the setting of poor disease control could increase risk of adverse pregnancy outcomes, disease progression, fetal compromise, or long-term childhood health issues. The postpartum period is an especially vulnerable time, as 70% of pregnancies that occur within 1 year of delivery are unplanned. Interpregnancy intervals shorter than 6 months are associated with increased risks of preterm birth, low birth weight, and small for gestational age infants.

Despite the need for pregnancy planning, medically complex women face many barriers to contraceptive use. Providing contraceptive counseling and a full range of contraceptive options, including immediate postpartum long-acting reversible contraception (LARC), is a means of overcoming these barriers.

LARC methods include hormonal and nonhormonal intrauterine devices (IUDs) as well as subdermal contraceptive implants. In the United States, the levonorgestrel intrauterine system (IUS) is available in several commercial preparations (Liletta, Mirena, Kyleena, and Skyla), and the nonhormonal copper IUD is commercially available as Paragard. The etonogestrel implant is commercially known as Nexplanon.

Q | What is the role of LARC in reproductive planning in medically complex women?
The American College of Obstetricians and Gynecologists (ACOG) recommends that LARC methods be offered to all appropriate candidates. LARC methods have low failure rates, similar to those of sterilization, making them appealing to women for whom future pregnancy is not recommended or when sterilization is not an option. For medically complex women, LARC methods provide the benefit of allowing a pregnancy to occur in a well-planned and highly supervised medical setting for women in whom an unplanned pregnancy would pose a high medical risk. The long-acting nature of LARC al-
Although immediate postpartum IUD has higher expulsion rates than interval placement, the benefits of immediate placement appear to outweigh the drawbacks.

allows women to optimize chronic health conditions prior to conception, but LARC methods remain easily reversible when pregnancy is desired. LARC methods do not contain estrogen, making them safe options for women with a history of medical conditions, such as thromboembolic disease, for whom estrogen is contraindicated.

Q | What is immediate postpartum LARC?
Immediate postpartum placement is defined as insertion of an IUD after placental delivery following a vaginal or cesarean delivery and insertion of an implant at any time during the delivery hospitalization.

Q | When should providers discuss immediate postpartum contraception?
Contraceptive counseling should begin early in pregnancy, be individualized, include a balanced discussion about the risks and benefits of all contraceptive methods, and use shared decision-making. Incorporating contraceptive counseling into prenatal care can contribute substantially to a woman’s health long after pregnancy. This should be an ongoing discussion during the prenatal period, as complications can develop during pregnancy that may have an impact on contraceptive counseling.

Q | What are the benefits of immediate postpartum LARC insertion?
LARC is a safe, convenient, and effective option for postpartum contraception that can be placed immediately after delivery. It provides immediate contraception without breastfeeding interference and avoids the discomfort related to later IUD insertion. Compared with short-acting methods, use of immediate postpartum LARC results in increased short-term contraceptive use, similar or increased long-term contraceptive use, and decreased prevalence of short interpregnancy intervals and rates of unintended pregnancy. Compared with other interval insertions of LARC methods, immediate postpartum placement is associated with high patient satisfaction and acceptability, increased method continuation, and superior cost-effectiveness.

Q | What are the contraindications to immediate postpartum LARC?
The few contraindications to immediate postpartum LARC placement are similar to those for interval LARC placement and are listed in the US MEC. Clinical recommendations and medical contraindications to LARC in the US MEC also apply to the immediate postpartum period.

Q | What are the risks of immediate postpartum IUD placement?
Most risks are similar between immediate postpartum IUD insertion and insertion at other times, with the exception of expulsion, which has a higher risk. Expulsion rates of 2%, 10%, and 25% have been reported with immediate postpartum IUD placement compared with expulsion rates of 2% with 6-week postpartum IUD placement. The expulsion risk may influence LARC choice for some women. Although immediate postpartum IUD placement has higher expulsion rates than interval placement, the benefits of immediate placement appear to outweigh the drawbacks. A review of seven studies shows that even with higher expulsion rates, women who had immediate postpartum IUD placement were more likely to continue to use the IUD at 6 months than those who had an IUD inserted at another time.

Q | What is the technique for immediate postpartum LARC placement?
Several techniques of immediate postpartum LARC placement following vaginal and cesarean delivery are described,
using either a ring or Kelly placental forceps, manual insertion with the operator’s hand, or the manufacturer’s inserter. ACOG suggests that providers receive formal training to enable appropriate immediate postpartum IUD placement after cesarean and vaginal deliveries. LARC method-specific training opportunities are available on the ACOG website (https://www.acog.org/About-ACOG/ACOG-Departments/Long-Acting-Reversible-Contraception and https://pcainitiative.acog.org/).

The technique for immediate postpartum contraceptive implant insertion is the same used in other settings and at other times. Insertion can be achieved in the labor and delivery unit or in the postpartum unit. The US Food and Drug Administration requires that obstetric care providers receive training provided by the manufacturer.

Q | Does immediate postpartum LARC placement inhibit breastfeeding?
Although there is theoretical concern that the progestogens in the hormonal IUS and contraceptive implant could impair the onset of lactogenesis in women receiving immediate postpartum LARC, no reduction in breastfeeding has been observed in randomized trials. Women considering immediate postpartum hormonal LARC should be counseled about the theoretical risk of reduction in breastfeeding, but that the preponderance of the evidence has not shown a negative effect on actual breastfeeding outcomes.

Q | What is “early postpartum” LARC placement?
Early postpartum LARC placement is defined as LARC insertion shortly after hospital discharge and within the first few weeks postpartum. The expulsion rate for early postpartum LARC placement is consistent with that for interval insertion and lower than that for immediate postpartum placement. In environments where immediate inpatient placement of postpartum LARC is not possible, a program of early postpartum placement has similar benefits and could provide similar reductions in unplanned and close-interval pregnancy.

### SUMMARY OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. We recommend that LARC be offered to women at highest risk for adverse health events as a result of future pregnancy.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>2. We recommend that obstetric care providers discuss the availability of immediate postpartum LARC with all pregnant women during prenatal care and consult the US MEC guidelines to determine methods most appropriate for specific medical conditions.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>3. We recommend that women considering immediate postpartum IUD insertion be counseled that although expulsion rates are higher than with delayed insertion, the benefits appear to outweigh the risk of expulsion, as the long-term continuation rates are higher.</td>
<td>1C Strong recommendation, low-quality evidence</td>
</tr>
<tr>
<td>4. We recommend that obstetric care providers wishing to utilize immediate postpartum LARC obtain training specific to the immediate postpartum period.</td>
<td>Best practice</td>
</tr>
<tr>
<td>5. For women who desire and are eligible for LARC, we recommend immediate postpartum placement after a high-risk pregnancy over delayed placement due to overall superior efficacy and cost-effectiveness.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>6. We recommend that women considering immediate postpartum LARC be encouraged to breastfeed, as current evidence suggests that these methods do not negatively influence lactation.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>7. For women who desire and are eligible for LARC, we suggest that early postpartum LARC placement be considered when immediate postpartum LARC placement is not feasible.</td>
<td>2C Weak recommendation, low-quality evidence</td>
</tr>
<tr>
<td>8. We recommend that the contraceptive counseling programs be patient-centered and provided in a shared decision-making framework to avoid coercion.</td>
<td>Best practice</td>
</tr>
</tbody>
</table>

**Q** What is the maternal-fetal medicine (MFM) subspecialist’s role in implementing immediate postpartum LARC programs?

MFM subspecialists are uniquely positioned to promote immediate postpartum LARC placement because of their frequent and in-depth contact with high-risk and medically complex women during pregnancy and the postpartum period. Pregnancy is a time of high motivation for contraception; this is especially true for women with complicated pregnancies who are receiving regular counseling about the maternal and fetal risks to their current and future pregnancies. Obstetric care providers can also advocate for their patients on both an individual and system-wide level.

**Q** How should patients be counseled about immediate postpartum LARC?

Counseling should be patient-centered and provided in a shared decision-making framework, should avoid coercion, and should include the option for sterilization as well as short-acting methods. This is particularly important for low-income women and women of color, who may be more susceptible to coercion and reproductive injustice. For women who want a future pregnancy, LARC should be encouraged as an option because of its superior efficacy and longer therapeutic window. It is important to explain IUD expulsion rates and to have a plan for contraceptive management, should expulsion occur. Anticipatory guidance about side effects such as vaginal bleeding can also be provided. Obstetric care providers can use their familiarity with their patients’ health histories to help patients choose a contraceptive method that is compatible with their medical restrictions. Evidence-based contraceptive educational tools can be used by providers to assist in counseling women.

**Q** What are the barriers to immediate postpartum LARC placement?

Health-care system issues are the primary barrier to widespread immediate postpartum LARC use. Coordinated programs involving cooperation among providers, administration, billing, and pharmacy services are not widespread. In some religiously affiliated hospitals, immediate postpartum LARC placement may be specifically prohibited. Lack of awareness or misperceptions among MFM subspecialists and general obstetricians can impede immediate postpartum LARC placement. Insurance coverage and payment difficulties are persistent obstacles to implementation of immediate postpartum LARC placement programs and are often the result of misinformation regarding LARC clinical effects. Although Medicaid reimbursement for LARC is increasing, inpatient billing processes remain unclear for many hospitals and are not well aligned with systems for absorbing the up-front cost of the devices. Insurance coverage of IUD reinsertion in cases of postpartum expulsion and access to and coverage for removal services are also concerns for both women and obstetric care providers.

**Q** What steps can be used to increase access to immediate postpartum LARC?

Obstetric care providers can encourage development of dedicated LARC placement teams to facilitate LARC access in both inpatient and outpatient settings. Dedicated LARC placement teams can counsel women and place LARC, provide estimates of demand and inventory stocking needs, and appropriately bill for services. Expanding the range of health care professionals, such as nurses or midwives, who are trained to counsel women and to insert LARC devices could reduce the burden on physicians. ACOG’s Postpartum Contraceptive Access Initiative provides technical assistance, resources, and free onsite training to support dedicated LARC placement teams (https://pcainitiative.acog.org/).

Obstetric care providers can advocate for their patients on both an individual and system-wide level. Support from MFM subspecialists and family planning experts could encourage hospital systems to develop guidelines for integrating immediate postpartum LARC into best practices that provide a policy framework for these services. Educating hospital administration about the safety, acceptability, and cost-effectiveness of immediate postpartum LARC can improve the likelihood of institutional support for a placement program.

Counseling high-risk women about postpartum contraceptive options may not be prioritized during management of a complicated pregnancy. LARC and other postpartum contraceptive methods may not be addressed because of lack of knowledge, lack of time, or the perception by referring or MFM subspecialist providers that it is not their role. However, discussing postpartum contraceptive options early and often can increase awareness of the role of immediate postpartum contraception in improving health outcomes and reducing unplanned and close-interval pregnancy.
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Alternatives to traditional surgery for fibroids

Experts provide an update on current and emerging drugs and procedures as an alternative to myomectomy for uterine leiomyomas.

by ELIZABETH A. STEWART, MD, AND MACKENZIE P. PURDY, MD

Uterine leiomyomas (fibroids) are benign smooth muscle neoplasms that affect up to 70% of women over their lifetime. They are the most common primary indication for hysterectomy and account for over $34 billion in health care costs annually in the United States. Common symptoms of fibroids include heavy or prolonged menstrual bleeding, pelvic pain, pressure-related symptoms, and bladder and bowel disturbance.

For the woman who wants to manage symptoms while maintaining her uterus or improve her fertility outcome, myomectomy has been considered the gold standard. However, there are substantial risks to myomectomy with overall reported complications in surgeon-reported series of 3% to 16% and 25% in analysis of an insurance claims database. Common complications include hemorrhage and transfusion (5% risk), and damage to other organs requiring a subsequent procedure (25%). Also for women desiring future pregnancy, many myomectomy procedures commit women to a cesarean delivery in future pregnancies, further increasing surgical morbidity.

In addition to complications, surgery can be expensive and require a significant recovery period with estimates from the literature of 15 to 30 days, and shorter recoveries in women who undergo endoscopic procedures. Moreover, because of the high rate of new fibroid formation, many women undergo multiple surgeries.

Rates of reintervention with a second uterine-sparing procedure are 22% and with a hysterectomy are 16.7% with 5-year follow-up based on claims data. With our increasing knowledge of fibroid biological development and technological innovation, we now have multiple alternatives to traditional surgery, including medical and less invasive procedural management that will be considered here. The Agency for Healthcare Research and Quality recently produced a comprehensive evidence report on fibroid therapies which comprehensively assesses this topic.

Medical management

Contraceptive steroids

Combined estrogen/progestin and progestin-only oral contraceptives
(OCs) have historically been seen as first-line therapy for fibroids due to their safety profile, low cost and reliable contraception. The levonorgestrel intrauterine system (LNG-IUS) is also being increasingly used for heavy or prolonged menstrual bleeding (AUB-L utilizing FIGO nomenclature); it also provides reliable contraception that does not require daily use. Surprisingly, high-quality data to support OCs or LNG-IUS for treatment of symptomatic fibroids are limited, as many studies do not have a proper comparison group. Observational data have demonstrated support for OCs. However, one randomized trial of 58 women demonstrated significantly decreased AUB-L in those treated with LNG-IUS when compared to OCs (mean menstrual blood loss decreased by 77.5% by extraction of blood from sanitary products and 34.5% by menstrual pictogram). Overall, we are still in need of better evidence demonstrating the superiority of contraceptive steroids.

**Progesterone receptor modulators**

Although classically estradiol (E2) has been thought of as the key hormonal influence of fibroid pathophysiology, both scientific investigation and clinical use of progesterone receptor modulators (PRMs) for fibroid treatment now suggest that progesterone is the major hormonal influence. In contrast to contraceptive steroids, PRMs have been studied in multiple randomized controlled trials (RCTs) and have shown moderate evidence for symptomatic relief, including reduction in fibroid size and decreased AUB-L and pain. Mifepristone and ulipristal acetate have been studied most commonly and there are 14 RCTs with more than 1200 participants demonstrating an improvement in quality of life. Thus, PRMs are widely used as first-line therapy outside the United States but are not approved by the US Food and Drug Administration (FDA).

While original reports focused safety concerns on endometrial changes following continuous use of PRMs, rare but serious liver injury has recently become the focus of safety with ulipristal acetate treatment as currently used in intermittent courses separated by shedding of the endometrium. New guidance had been issued by the European Medicines Agency (EMA) based on serious events involving the liver, in some cases requiring liver transplantation, occurring in approximately 1:100,000 women (https://www.ema.europa.eu/en/medicines/human/referrals/esmya). This guidance requires screening women for liver dysfunction with both history and liver function tests before, during, and after treatment. Finally, the guidelines recommend restricting ulipristal acetate to one treatment course in women who are eligible for surgery.

**Gonadotropin-releasing hormone (GnRH) agonists/antagonists**

GnRH agonists exert their effect by having a higher potency and longer half-life than endogenous GnRH, which when used in a recurring manner leads to prolonged binding to its receptor. This initially leads to an increase in FSH and LH secretion from the anterior pituitary and subsequently a flare in estrogen production followed by suppression. GnRH agonists have shown a reduction in fibroid volume and improvement in AUB-L along with an improvement in quality of life. Concerns with long-term treatment with GnRH analogues stem from evidence showing a decrease in bone mass after 4 to 6 months of therapy along with significant hypooestrogenic side effects that include vasomotor symptoms, atrophic vaginitis, and insomnia, which occurs due to the hypothalamic-pituitary-ovarian axis blockade. The GnRH agonist leuprolide acetate is FDA-approved for short-term use in treatment of uterine fibroids in conjunction with iron for preoperative treatment. Add-back therapy with different modalities (raloxifene, conjugated estrogens, estriol) can be useful in preserving bone density but there is limited evidence that this leads to improvement in hypooestrogenic symptoms. In addition, after discontinuation of therapy, fibroid growth will typically resume, leading to a return in original size or beyond.

In contrast to GnRH agonists, GnRH antagonists exert their effect by competing for the GnRH receptor and thus have a more rapid onset without the initial flare. GnRH antagonists for fibroids demonstrated a significant reduction in tumor volume but require daily treatment. A new generation of oral GnRH antagonists used either alone or with hormonal add-back therapy is in clinical trials.
for treatment of uterine fibroids. A recent noninferiority trial demonstrated more rapid onset of amenorrhea with an oral GnRH antagonist (relugolix) and similar reductions in AUB-L and uterine volume when compared to leuprolide acetate. An RCT evaluating add-back therapy with a second oral GnRH antagonist (elagolix) demonstrated a continued reduction in AUB-L and add-back therapy reduced negative effects on bone mineral density.

Procedural management

Uterine artery embolization

Uterine artery embolization (UAE) utilizes a single small incision in the groin and radiographic guidance of catheters and embolic agents to the uterine arteries bilaterally. Thus multiple fibroids can be targeted simultaneously. UAE requires sedation and typically is performed as an overnight admission or same-day procedure.

Multiple RCTs have demonstrated the efficacy of UAE in women with fibroids. The quality of evidence has been high for a significant volume reduction that continued for 5 years and improvements in AUB-L along with moderate evidence for an improvement in quality of life. When compared to hysterectomy and myomectomy, risk of transfusion with UAE was drastically reduced (OR 0.07, 95% CI, 0.01-0.52). Women undergoing UAE also recovered more rapidly and had fewer major complications, but more minor complications requiring no or nominal therapy, including overnight admission for observation, were noted when UAE was compared to hysterectomy but not when compared to myomectomy. In the RCT between UAE and hysterectomy, postembolization and vaginal discharge were the most frequent minor complication following UAE and infection and hemorrhage the most common following hysterectomy; the median length of stay was 1 day for UAE and 5 days for hysterectomy possibly affecting readmission for observation.

Concerns regarding UAE are associated with a higher rate of subsequent surgical intervention with estimates of 7% for myomectomy and hysterectomy versus 15% to 32% for UAE. However, studies have not reported whether failures of UAE are due to concomitant diseases such as adenomyosis, which is also treated with hysterectomy but not uterine-sparing approaches. In a study based on insurance claims, the chance of a complication requiring a subsequent procedure was substantially higher following myomectomy compared to UAE in a propensity-matched group (24.6 vs. 18.1%, HR 1.38 (95% CI, 1.25-1.52)). Concerns regarding UAE are associated with a higher rate of subsequent surgical intervention with estimates of 7% for myomectomy and hysterectomy versus 15% to 32% for UAE. Studies have demonstrated there is no significant difference in ovarian failure rates at long-term follow-up and there is very-low-level evidence that there is a decrease in fertility following UAE compared to myomectomy. Finally, there are numerous reports of successful pregnancy following UAE and some national guidance recommending UAE for fertility preservation.

Focused ultrasound

High-intensity focused ultrasound ablation (HIFU) is a noninvasive method that uses ultrasound energy to create coagulative necrosis in a well-defined area through the anterior abdominal wall. HIFU can be performed under magnetic resonance imaging (MRI) or ultrasound guidance; however, only the device that uses MRI guidance is approved in the United States. Both procedures are performed on an outpatient basis with sedation and no incisions.

Overall, HIFU has been shown to be effective for decreasing fibroid size/volume. Recent investigation has shown that other important patient outcomes are also improved. A large cohort study compared 1353 women undergoing ultrasound-guided HIFU to hysterectomy (N=472) or myomectomy (N=586). Quality of life improved more quickly after HIFU compared to surgical intervention and HIFU had only 0.2% major adverse outcomes compared to 12.6% in the surgical cases (P < 0.001). Despite multiple differences in patient demo-
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Breastfeeding

...rational users and levels are extremely varied and have been found in the urine of breastfeeding infants 24 to 36 hours after maternal use. The elimination half-life is 1 hour, and concentrations are eight times higher in breastmilk than in the plasma of the user. Infants are extremely sensitive to cocaine because of immature inactivation enzymes (plasma cholinesterase). Infants exposed to cocaine in breastmilk exhibit irritability, tremulousness, dilated pupils, hyperextension, seizures, vomiting, high pitched crying, and respiratory distress. Infant deaths have been reported. Breastmilk should be pumped and discarded for 24 hours after use, which may be impractical. Mothers using cocaine who do not enter treatment or cannot manage harm reduction strategies should be counseled not to breastfeed.

Methamphetamine or MDMA

Amphetamine-type stimulants easily cross into breastmilk and are concentrated there in higher amounts (3-8 times) than in the plasma of the user. The elimination half-life is 6 to 12 hours. Infants breastfed by amphetamine users experience irritability, poor sleeping, agitation, and excessive crying. Infant deaths from cardiopulmonary failure have been reported. Milk should be pumped and discarded for 48 to 100 hours after use, which is impractical. Mothers using methamphetamine or MDMA who do not enter treatment or cannot manage harm reduction strategies should be counseled not to breastfeed.

Marijuana

The psychoactive compound in marijuana, delta-9-tetrahydrocannabinol (THC), accumulates in breastmilk in moderate to severe amounts depending on chronicity of use. The elimination half-life is 20 to 36 hours and up to 4 days in chronic users. Data are insufficient on which to base conclusions about the long-term effect of marijuana exposure through breastmilk. As a result, use of marijuana is discouraged during breastfeeding. Benzodiazepines

One-third of benzodiazepine (BZD) use is illicit. BZDs appear in low concentration in breastmilk at about half of maternal plasma levels. Short- and intermediate-acting BZDs like alprazolam and lorazepam, respectively, provide negligible infant exposure and have not been associated with problems. Long-acting BZDs like diazepam have the potential to cause lethargy, sedation, and weight loss in infants, which are reversible after breastfeeding is discontinued, although abrupt weaning or rapid cessation can precipitate withdrawal in the infant. Breastfeeding is not recommended with long-term or high-dose use of long-acting BZDs or when using multiple sedative drugs. For occasional use, milk should be pumped and discarded for 6 to 8 hours after use. Alcohol

Half of breastfeeding women in western countries reportedly consume alcohol at least occasionally. Alcohol interferes with the milk ejection reflex and may reduce production. Human milk levels parallel maternal blood alcohol levels. Long-term effects of alcohol exposure in breastmilk are unknown. Most experts advise limiting alcohol intake to only 8 oz of wine or two beers and to wait for 2 hours after drinking to resume breastfeeding.

Tobacco

Nicotine is concentrated in breastmilk in concentrations up to three times maternal plasma although only 10% is excreted into breastmilk. The elimination half-life of nicotine is approximately 2 to 4 hours. There is no evidence that nicotine in breastmilk represents a health risk to the infant and breastfeeding benefits are thought to outweigh risks. Other chemicals in secondhand smoke are thought to be worse and increase incidence of respiratory allergy and sudden infant death syndrome (SIDS). Tobacco smokers are encouraged to breastfeed while trying to quit, start nicotine replacement, and eliminate infant smoke exposure.

Conclusion

Neonates of mothers with SU and SUD who can be breastfed stand to gain significant benefits as do their mothers, who may use motherhood and breastfeeding as a chance to change the path of their lives. With appropriate non-judgmental support, mothers with SU and SUD can achieve breastfeeding success. Caring for these patients also offers ob/gyns potential opportunities for growth and for overcoming intrinsic biases and other barriers.

DISCLOSURES

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

FOR REFERENCES VISIT contemporaryobgyn.net/BreastfeedingSubstance
Seven surgeries, one lawsuit
CONTINUED FROM PAGE 49

with a simple cyst. The patient was placed on oral estrogen replacement.

A month after the laparoscopy (2 months after the hysterectomy), the woman was seen by her psychiatrist and diagnosed with enhanced anxiety and post-traumatic stress disorder (PTSD). A fourth psychotropic medication was added, as she continued to see her psychiatrist on a monthly basis.

Nine months after the hysterectomy and 8 months after the BSO the patient was seen for complaints of intermittent stress urinary incontinence for 2 months, with pressure in the vagina. Examination revealed a thin rectovaginal septum and a probable cystocele. She was scheduled for surgery, with her preoperative history documenting “… progressive debilitating loss of urine, minimal valsava, unable to handle daily activities…” The documented consent discussion in the office consisted of, “Risk & benefit ready.” Three weeks later the patient underwent a cystourethropexy and a posterior colporrhaphy, complicated by a 1200-mL blood loss requiring transfusion. She was discharged with an indwelling catheter, which was removed 1 week later with a postvoid residual (PVR) less than 100 mL. She had a mildly odiferous vaginal discharge that was treated with metronidazole vaginal gel.

The patient was seen in the emergency department (ED) 1 week after the catheter was removed, complaining of bladder pain and abdominal distension. She was found to have acute urinary retention and an indwelling Foley catheter was placed. Three days after the ED visit, the woman was seen by her gynecologist, who noted that a urine culture obtained in the ED revealed *Klebsiella pneumoniae* > 1000,000 col/mL. The patient was treated with nitrofurantoin. Because she had a PVR of 140 mL, a catheter was reinserted; a CT and ultrasound also were ordered. The CT revealed a pelvic abscess or hematoma. The ultrasound revealed a seroma, with no evidence of an abscess. The patient was referred to a urologist for further evaluation.

One week later, the urologist evaluated the patient and diagnosed urinary retention, chronic abdominal distension, and depression. An intravenous pyelogram (IVP) was normal without significant PVR. The catheter was removed, and the patient was instructed in self-catheterization, which she performed twice a day. Three weeks after the initial appointment with the urologist, she underwent cystourethrocystoscopy, which found significant residual urine, no sutures visualized in the bladder, and both ureteric orifices seen. She then underwent complex urodynamics, which showed a PVR of 500 mL; the diagnosis was primary vesical neck contracture and bladder outlet obstruction. One week later, the patient underwent cystoscopy and urethral dilatation. Ten days after that, she was seen in the ED with acute urinary retention. Of note, during her monthly appointment with her psychiatrist, the patient expressed anger with her gynecologist. She continued with self-catheterization. One month after the urethral dilatation, the patient underwent cystoscopy, urethrolysis and urethral dilatation in the operating room, during which the urethra was noted to be elevated well beyond the horizontal and in close apposition to the pubic bone.

Ten days after her most recent surgery, the patient was again seen in the ED with acute urinary retention (PVR = 1000 mL). A urine culture revealed *Klebsiella pneumoniae* > 100,000 col/mL, which was treated with levofloxacin. The patient continued to have urinary retention that was unresponsive to additional dilatation. Seven months after the original cystourethropexy, she underwent an open revision of the suspension by the urologist, but her urinary retention persisted and she required ongoing self-catheterization.

The patient then developed chronic constipation and was referred to a gastroenterologist, who found decreased innervation to the pelvic area, causing urinary retention, obstipation, and fecal impaction. It was postulated that the absent sphincter tone could be secondary to the patient’s psychotropic medications.
The patient sued her gynecologist for performing unnecessary surgery (the hysterectomy), improperly performed surgery (the cystourethropexy), and subsequent complications that required six additional surgeries, with resultant unrelenting urinary retention, obstipation, and PTSD.

At trial, the plaintiff’s expert, an academic urogynecologist, testified that the hysterectomy was performed without an adequate trial of medical therapy, supported by the lack of significant pathologic findings. Complications from the hysterectomy led to a second surgery, which resulted in the patient, at a relatively young age, requiring long-term hormonal therapy. In addition, the cystourethropexy was performed without an appropriate evaluation or trial of medical therapy. He testified that the preoperative counseling and informed consent were inadequate. He opined that the procedure performed had largely been replaced by less invasive procedures, which have fewer complications. The cystourethropexy was improperly performed with the urethra elevated too high, resulting in persistent urinary retention, unresponsive to six surgical procedures. Further, there were no documented symptoms to justify the posterior colporrhaphy. As a result of these unnecessary procedures, the patient had refractory urinary retention and obstipation. A psychiatrist for the plaintiff testified that, although the patient had preexisting depression and anxiety, her PTSD was directly related to or significantly exacerbated by the complications and multiple surgeries without relief of her symptoms. Further, surgery should be approached cautiously in all patients, but particularly

ANALYSIS

The gynecologist was very fortunate to receive a favorable verdict. The case demonstrates the fact that most physicians are held in high regard and juries tend to give them the benefit of the doubt. As a result, most cases are found in favor of the defendant physician, occasionally even with overwhelming evidence against them. One must be cautioned that the jurisdiction, or location, of the trial can have a tremendous impact on the verdict. Even with the same facts, some jurisdictions are more favorable for physicians than others.

However, this case demonstrates several opportunities for learning:

1. Surgical procedures should be considered only after adequate evaluation and treatment with medical therapy or less invasive procedures.

2. Gynecologists should remain abreast of currently available procedures, particularly when less invasive procedures are available. In this case, midurethral slings have replaced open cystourethropexy, except in unique cases. If a patient is a candidate for a less invasive procedure that the physician does not perform, he or she should consider referring the patient to a surgeon with the expertise.

3. Repair of asymptomatic vaginal relaxation, or in this case an asymptomatic thin rectovaginal septum, is not recommended.

4. Informed consent was lacking, or at least appropriate documentation was lacking. The actual informed consent document is intended to memorialize the culmination of discussions between the patient and her physician, providing the patient enough information to make an informed decision about her care and treatment. In general, such documented discussions should address: 1) the diagnosis; 2) the planned procedure or treatment; 3) alternatives to the procedure, including medical therapy and even doing nothing; and 4) the substantial complications that could result from the surgery.

5. Patients with underlying psychiatric conditions, particularly those requiring multiple medications and chronic psychiatric care, require special attention when contemplating major surgical procedures. It may be prudent to have the patient seen by her psychiatrist or psychologist prior to surgery, and to assess any post-surgical changes in psychiatric status.

6. A malpractice suit may be a patient’s only way to pay the medical bills resulting from complications, some of which can be overwhelming. This particular patient had seven surgical procedures following the vaginal hysterectomy. With a defense judgment, the patient and her family had no option but to declare bankruptcy. As physicians, we must be sensitive to the impact our actions and recommendations have on a patient’s life.
in those with significant psychiatric symptoms, requiring frequent visits and multiple medications.

The defense’s expert, a rural gynecologist, testified that the numerous surgeries were the result of over-distention following surgery. He could not cite any history to support a diagnosis of stress urinary incontinence. He stated that the patient had a normally functioning bladder with an outlet obstruction. He could not reference any history supporting performance of the posterior colporrhaphy.

The defendant stated that he never performs a procedure based on one report of a problem. He was then forced to admit that he performed a hysterectomy based upon only one office visit. He also could not explain his note that he had 1½ years of discussions with the patient regarding the problems, nor the lack of any written documentation. He further admitted that his admission history and physical for the bladder surgery were done purely from memory, based on his examination 3 weeks prior. He could not cite any documentation of symptoms justifying the posterior colporrhaphy.

Ultimately, the jury rendered a verdict for the defendant. Following the trial, the patient filed for bankruptcy.

Fibroids CONTINUED FROM PAGE 40

graphics between the treatment groups, with the patients undergoing HIFU being younger, better educated, and wealthier compared to the surgery groups, the authors concluded there is less morbidity when patients undergo HIFU compared to surgery. A case control study analyzing approximately 10,000 women who underwent HIFU demonstrated successful rates of ablation with a mean volume ablation rate of 83.1% ± 15.6% (range, 25%-100%) for patients with fibroids.

The authors found that with conscious sedation and analgesia there were minimal side effects and very few severe complications. Case series have documented successful pregnancy outcomes following MRgFUS.

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow (FIRSTT) study analyzed patients randomized into UAE or MRgFUS groups and a parallel group declining randomization. Both groups had improved fibroid symptoms and quality of life for up to 2 years but improvement was significantly better for women who underwent UAE and risk of needing another fibroid procedure was higher (HR 2.81, 95% CI, 1.01-7.79, P = .047) for women undergoing MRgFUS.

Radiofrequency ablation (RFA)

Introduced in 1999, laparoscopic, intra-abdominal-guided radiofrequency ablation (RFA) is another surgical modality developed to be less invasive. Benefits of this procedure include ease of use as it does not require laparoscopic suturing and there is no dissemination of tissue in the abdomen, which can occur with laparoscopic hysterectomy/myomectomy. A RCT by Bruker et al. demonstrated a shorter hospital stay and decreased blood loss when comparing RFA to laparoscopic myomectomy. While this is an attractive option we have limited evidence about long-term outcomes for RFA and it still requires a laparoscopy. A transcervical, intrauterine sonography-guided RFA device has been studied and is approved for use outside the United States but is not FDA-approved.

Conclusions

In the not too recent past, surgical intervention represented the only strategy for symptomatic and/or large fibroids. With our growing appreciation of high fibroid incidence and burden, we are continuing to develop less-invasive strategies to improve symptoms and patient quality of life. Overall, there is good evidence that demonstrates that GnRH agonists and PRMs result in reduction of fibroid volume and improvement in quality of life for women with fibroids. UAE has also been shown to reduce uterine and fibroid volume with improvement in quality of life with more data needed to verify the procedure’s safety in patients planning to conceive in the future. While OCs have been first-line therapy in the past, there is a paucity of data supporting their benefit and, therefore, other strategies should be explored. Lastly, HIFU has been shown to reduce fibroid volume but more rigorous studies are needed to determine long-term outcomes and assess fertility following treatment.

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

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When seven surgeries equal one lawsuit

Multiple gynecologic surgeries led to legal action with a surprising outcome.

A 37-year-old G6P5015 with irregular menstrual and some right lower quadrant pain presented to her gynecologist for her annual examination. The patient’s examination was normal as was pelvic ultrasound she had approximately 2 months before this appointment. The plan was to obtain another pelvic ultrasound and, if negative, place the patient on oral contraceptives for 2 months. No medical therapy or follow-up was documented.

The patient’s past medical history was significant for four prior laparoscopies: one for a possible ectopic pregnancy (not confirmed, with decreasing quantitative hCG levels); one for sterilization, with a normal pelvis documented; and two for pelvic pain, one demonstrating a “window” in the posterior broad ligament. Also, the patient had a history of fibromyalgia, anxiety, and depression, which required treatment with three different psychotropic medications. She saw her psychiatrist monthly.

Eighteen months later, the patient was seen for another “annual” examination. She had complaints of heavy vaginal bleeding. The examination revealed a “retroverted uterus, of top-normal size, descending to 1 cm above the introitus.” A thinning rectovaginal septum was noted. The following plan was documented, “Schedule vaginal hysterectomy. Risks and benefits have been reviewed and these have been discussed over the past year-and-a-half since tubal ligation. These symptoms are unremitting to conservative medical modalities. The patient wishes to proceed with surgical intervention.” No documented examinations or discussions since the previous examination, 18 months earlier, were noted. The patient was referred to her psychiatrist for evaluation prior to surgery.

One month later, the patient underwent a total vaginal hysterectomy with removal of Hulka clips. Pathology revealed a 112-g uterus with proliferative endometrium, no adenomyosis or myomas, chronic endocervicitis, and the Hulka clips. Two weeks later the woman was admitted for cuff cellulitis, which was treated with antibiotics. One week after this second admission, she was seen in the physician’s office with persistent pain and discomfort. Computed tomography (CT) revealed a 5 x 7 cm tubular mass in the left adnexa, with a differential diagnosis of a lymphocele, tuboovarian abscess, or cystic mass of left ovary.

Two weeks later the patient underwent laparoscopic adhesiolysis of omental adhesions covering the left ovary and bilateral salpingo-oophorectomy (BSO). Pathology revealed only one tube, which was normal, with normal ovaries bilaterally, one

The plan was to obtain another pelvic ultrasound and, if negative, place the patient on oral contraceptives for 2 months.

Dr. Shwayder is Professor of Obstetrics and Gynecology and former Chair at the University of Mississippi Medical Center. He is a graduate of the University of Denver College of Law and is a nationally and internationally recognized expert in gynecology ultrasound and minimally invasive surgery. He actively consults on legal matters in medicine, including liability in ultrasound and gynecologic surgery, as well as issues surrounding privileging and insurance fraud.
fFN + TVUS dramatically increases sPTB prediction

Risk of sPTB <7 days in patients with symptoms of preterm labor

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The Role of Hysteroscopy in Managing Miscarriage
The Role of Hysteroscopy in Managing Miscarriage

Panelists
Aaron K. Styer, MD, is a board-certified reproductive endocrinologist, founding partner, and medical director of CCRM Boston in Chestnut Hill, MA. He is also a staff physician at Beth Israel Deaconess Medical Center and is an associate professor of obstetrics, gynecology, and reproductive biology at Harvard Medical School. Dr. Styer is nationally recognized for his expertise in elective single embryo transfer, predictors of IVF success, LGBTQ family building, egg donation, and fertility outcomes in women with uterine fibroids and endometriosis. Dr. Styer is active in patient outcomes research and education. He serves on several national committees in reproductive medicine, including the Society for Assisted Reproductive Technology Clinical Online Reporting System research committee, and is an active member of the Patient Education Committee of the American Society for Reproductive Medicine.

Zev Williams, MD, PhD, is chief of the Division of Reproductive Endocrinology and Infertility and the Wendy D. Havens Associate Professor of Women’s Health at Columbia University Irving Medical Center in New York, NY. A nationally recognized clinician and researcher in the area of recurrent pregnancy loss and infertility, Dr. Williams leads the Columbia University Fertility Center. While at Albert Einstein College of Medicine in New York, Dr. Williams established the Program for Early and Recurrent Pregnancy Loss (PEARL), which involves a clinical care site focused on a multidisciplinary approach to preventing recurrent miscarriage as well as a basic/translational research program. The PEARL program focuses on public education surrounding pregnancy loss, including webinars, public lectures, online informational videos, and online blogs.

Disclosures
All faculty, planning committee members, editors, managers, and other individuals who are in a position to control content are required to disclose any relevant relationships with any commercial interests related to this activity. The existence of these interests or relationships is not viewed as implying bias or decreasing the value of this publication.

AARON STYER, MD, has a financial affiliation with Medtronic (consultant).

ZEV WILLIAMS, MD, PHD, has a financial affiliation with Medtronic (consultant).

SCOTT KOBER, MBA (MEDICAL WRITER), has disclosed that he has had no relevant financial relationships specific to the subject matter within the last 12 months.

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IN TODAY’S SOCIETY, approximately 15% to 25% of pregnancies will end in miscarriage.1 Miscarriages can occur for a variety of reasons, including genetic abnormalities, medical conditions, and lifestyle choices (Table). Recurrent pregnancy loss, meaning miscarriages in two or more pregnancies, is less common, but still represents approximately 5% of all miscarriages.1

While determining the cause of any miscarriage is important, it is especially vital in women with recurrent pregnancy loss who remain interested in future conception. In this supplement, two experts in the management of miscarriage discuss the steps they take to uncover the underlying cause of recurrent pregnancy loss and the importance of hysteroscopy in finding the answers physicians and patients need.

<table>
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<th>TABLE: Common Causes of Recurrent Pregnancy Loss</th>
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Moderator: How do the majority of women end up in your practice following miscarriage?

Aaron Styer, MD: The most common means by which women come to my practice after miscarriage include referral from their ob/gyn or through an Internet search of fertility specialists who have expertise in managing recurrent pregnancy loss. Many patients are referred by word of mouth from the community as well. These women are typically referred to me by former or current patients.

Zev Williams, MD, PhD: The patients I see are typically those who have had a fair number of pregnancy losses for which the underlying etiology is unknown. The work that we do here focuses on trying to understand these really challenging cases of unexplained pregnancy loss, to figure out why they’ve been happening, and then put together a plan to help prevent them in the future.

Moderator: At what point do you recommend to your colleagues that they send challenging cases to a specialist like yourself?

Dr. Williams: There are high-quality standard protocols that both the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists have put out for the basic evaluation of a pregnancy loss.1,2 When that basic approach fails to identify the cause, that’s typically when it’s helpful to look at a deeper level for possible underlying causes.

I have seen patients for the first time who have had more than six miscarriages, although I would typically recommend referring patients with approximately three losses to a specialist when the initial workup fails to identify a cause.

Dr. Styer: Most frequently, colleagues will wait to refer their patients to me until two or more miscarriages have occurred. Some providers will refer earlier due to a specific patient request, if a patient has suffered a miscarriage in later stages of the first or second trimester of pregnancy, or if the patient is older than age 40 years and has diminished ovarian reserve.

Managing missed miscarriage

Moderator: When you have a woman who arrives in your office after a missed miscarriage, or multiple missed miscarriages, what does your initial workup look like? What is included within the evaluation?

Dr. Styer: Prior to diagnostic testing, the initial step is to ensure that the miscarriage has resolved and that all products of conception (POC) have been passed. This is usually confirmed by the patient’s referring ob/gyn or provider. During initial consultation, I also review the typical causes of miscarriage, discuss our approach for testing, and review the possible limitations of testing.

Initial testing will determine the karyotype of the patient and her partner (if she has a male partner) and will evaluate autoimmune and clotting factors. An essential step is to evaluate the endometrial cavity with hysteroscopy to ensure that the uterine cavity has healed appropriately and that there are no retained products of conception (RPoC). Concurrently, an endometrial biopsy is performed to exclude chronic endometritis.
Dr. Williams: In order for a pregnancy to succeed, a remarkable number of processes have to happen correctly. Perturbation or an abnormality during any of these processes can result in pregnancy loss and perhaps recurrent pregnancy loss.

When a new patient comes to our practice, our approach is to very systematically look at all the different steps that have to go right, to try to identify where the problem lies, and then to target the intervention to correct that problem. With the advances we’ve seen in terms of understanding the causes of pregnancy loss and the tools we have available to help identify those causes, we are currently able to determine the cause of pregnancy loss in approximately 90% of all cases. That’s a big improvement from a decade or so ago, when close to half of all cases of pregnancy loss were unexplained.

Moderator: What are the primary treatment options available to women with a missed miscarriage?

Dr. Williams: In women with a missed miscarriage, frequently called a missed abortion, they are typically offered the initial choice of expectant versus medical versus surgical management in my practice. Surgical management can involve either manual vacuum aspiration, which does not require anesthesia, or a traditional suction dilatation and curettage (D&C), which does. In cases in which there is a concern for the presence of adhesions, a hysteroscopically targeted removal of the gestational sac may be warranted.

One of the key factors when evaluating pregnancy loss is to determine if the loss is due to genetic factors or something else. If there is a clear genetic anomaly that is the overriding determinant, it’s critically important to obtain a sample from the pregnancy loss POC. While it is possible to obtain POC from miscarriage tissue that passes spontaneously or after medical intervention, there is a much higher likelihood of successfully obtaining POC through a surgical intervention. That is a key consideration when discussing treatment options.

Dr. Styer: From my perspective, the medical management of miscarriages with misoprostol and/or mifepristone is utilized more commonly than in prior years. However, I have seen similar rates of RPOC among patients undergoing medical treatment versus surgical treatment with D&C. As a result, I use the same approach of diagnostic office hysteroscopy for referred patients treated with either option.

Hysteroscopy in miscarriage

Moderator: When is hysteroscopy indicated following miscarriage?

Dr. Williams: Hysteroscopy is a tool that can give us additional useful information. For example, if there’s a concern that a patient has a uterine septum that may not have been resected, hysteroscopy allows you to determine exactly where the embryo implanted. There is also a role for hysteroscopy to help identify gross morphologic abnormalities that may point to a genetic basis for the miscarriage that can’t be readily detected with traditional approaches. Finally, in cases in which a patient has a history of RPOC or adhesion development, removing the gestational sac under direct visualization may offer benefit.

Dr. Styer: Routine pelvic ultrasound or sonohysterogram does not provide the same level of optimal detection of RPOC compared to direct visualization that is standard with office hysteroscopy. In my fertility practice, the clinical goal is always to optimize the chance of implantation prior to beginning fertility treatment. To this end, initial hysteroscopy as part of the evaluation of the uterine cavity following pregnancy loss is ideal to ensure that we exclude all barriers to future pregnancy success.

Moderator: Specifically, in women with RPOC, why is a hysteroscopically-guided procedure potentially a better treatment option than a blind or ultrasound-guided D&C?

Dr. Williams: The concern with suction D&C is that, when it’s done without direct visualization, there can be either too much tissue removed that results in adhesions or too little tissue left behind that does not pass spontaneously and leaves a woman at higher risk of subsequent pregnancy loss.

The advantage of a hysteroscopically-guided procedure is that it allows you to remove tissue under direct visualization so you can be more confident that you have removed all of the RPOC. Suction D&C can result in incomplete resection of the tissue and uterine adhesions.

Moderator: How commonly will women who have had a previous D&C following one or more miscarriages be referred to your practice?

Dr. Styer: I would estimate that about 50% of the women referred to my practice have had a D&C, while the remainder have been treated by medical management. That treatment choice can be driven by a variety of factors, including patient characteristics and preferences, patient history, as well as the experience and preference of the treating ob/gyn.
Moderator: Are there any potential advantages of a suction D&C compared to a hysteroscopically-guided procedure in women with RPOC after miscarriage?

Dr. Styer: In my opinion, there are no obvious advantages of suction D&C compared to hysteroscopic removal of RPOC. The risks of damage to the uterine lining following a D&C are increased compared to a hysteroscopic approach. Especially for women who wish to conceive in the future, minimizing inadvertent damage to the endometrium is a primary goal.

Genetic testing following miscarriage

Moderator: When is genetic testing indicated following miscarriage?

Dr. Styer: Genetic testing assists in determining if a patient and couple have a normal complement of chromosomes. In approximately 70% of cases, sporadic pregnancy loss is due to an abnormal chromosomal makeup of the embryo/fetus. Consequently, it is essential during the initial workup to first determine if the parents have any karyotypic abnormalities. If this testing is normal, genetic testing of the POC may detect genetic abnormalities.

Tissue samples are typically obtained by sampling POC after a D&C or hysteroscopically-guided procedure. Once tissue is removed, it can be sent for cytogenetic/karyotyping evaluation or gene array analysis. Gene array analysis has been recently implemented in clinical practice and most accurately detects genetic abnormalities in POC.

Dr. Williams: One of the great advances that has happened in recent years is the ability to do direct testing on DNA from POC. That avoids the need to have to culture fetal cells. Culturing fetal cells was often a problem because the cells that were collected would sometimes turn out to be maternal cells instead of fetal cells, or the tissue would not be of sufficient quality to culture any fetal cells. Now that we can extract DNA directly from POC, we have a much higher likelihood of getting genetic information and answers following a pregnancy loss.

Moderator: Do you typically order genetic testing in all of the women who come into your practice following a miscarriage?

Dr. Williams: Yes, but remember that the majority of my patients are women who have had multiple cases of pregnancy loss. Nonetheless, my personal feeling is that genetic testing may be helpful even after a first or second loss. There is often a tremendous sense of self-blame and guilt among women who suffer a pregnancy loss, even though we know that most cases are due to genetic anomalies and have nothing to do with anything the woman did wrong. It’s quite common that the couple will blame themselves for the loss. Being able to present them with genetic information showing that the fetus was abnormal at the moment of fertilization and was never destined to become a healthy delivery can bring a sense of closure and relief to the couple.

Choosing a hysteroscope for your practice

Moderator: What is your hysteroscopic resection device of choice, and why is that your preference?

Dr. Williams: I use the TruClear™ system by Medtronic. It allows me to get excellent visualization of the uterine cavity while simultaneously removing and extracting tissue. That allows me to avoid having to enter and exit the uterine cavity multiple times to remove the full tissue, which not only keeps operating time down but also reduces the risk of introducing an infection into the uterus. For smaller uterine lesions and polyps, I’ll often go in hysteroscopically and use the TruClear™ system as a resection device to manually remove tissue.

Dr. Styer: I also use the TruClear™ system for multiple clinical indications. I prefer to use this system due to the ease of setup, in either the office or the operating room, for our staff. From the patient perspective, the size of the hysteroscope is small enough that there is minimal need to dilate the cervix.

The ability to directly visualize and quickly resect tissue/pathology with the TruClear™ system is excellent, especially compared to typical procedures in which scissors or a grasper are used, making it difficult to efficiently remove tissue/pathology in its entirety. Most importantly, the design of the resection blade allows for removal of only the necessary pathology or abnormal tissue and minimizes unnecessary trauma to surrounding normal endometrial tissue.
**The Role of Hysteroscopy in Managing Miscarriage**

**Moderator:** Are there any other unique features of the TruClear™ system that you find to be particularly useful?

**Dr. Styer:** First, the coupled fluid management system and resection device allow for removal of pathology with concurrent suction of pathology and blood/debris. This provides excellent visualization in the field of resection. Also, the overall efficiency of the TruClear™ system as a resection device facilitates the removal of tissue/pathology quickly and in an atraumatic fashion. The TruClear™ system allows the surgeon to remove pathology without damaging or inadvertently resecting the normal endometrium that is adjacent to the pathology of interest.

**Dr. Williams:** One other thing I particularly appreciate about the TruClear™ system is that it allows me to enter the uterus without the need for electrocautery.

**Moderator:** For those providers who have little or no experience with a hysteroscope, how would you recommend they go about learning more about the technical aspects of its use?

**Dr. Williams:** The evidence is accumulating that in cases of RPOC among women who have had a miscarriage, especially those who have had a previous D&C, there are advantages to being able to directly visualize the tissue at the time of removal. For clinicians interested in learning more about the technical aspects of hysteroscopy, there are videos online that are very good. I’d also encourage them to speak to their colleagues and perhaps observe live cases so that there is a greater comfort level when they are doing procedures on their own. It may even be helpful having an experienced colleague at their side for the first few cases.

**Dr. Styer:** For the reproductive surgeon committed to operative hysteroscopy, the TruClear™ system is the ideal device for several reasons. The entry into the uterus is very straightforward. And as I mentioned previously, the TruClear™ system allows the surgeon to remove pathology quickly with optimal direct visualization of the uterine cavity.

As with any device clinicians use for the first time, there is a learning curve with the TruClear™ system. The learning curve is not steep, however, and the clinical use of the device is intuitive for either the attending physician or the trainee.

**Moderator:** This has been a terrific discussion. We want to thank both of you for your insights. I hope that our audience is able to take away some helpful information from our discussion to inform their practice’s approach to the use of hysteroscopy in the management of miscarriage.

**Key Takeaways**

- Following miscarriage, clinicians should ensure that there is complete passage of POC from the intrauterine cavity. Just because a patient’s human chorionic gonadotropin levels fall below zero does not necessarily mean that there are not RPOC.
- Particularly in cases of unexplained miscarriage, collecting as much information as possible in terms of the location and appearance of the gestational sac and uterus can be very informative.
- In women with RPOC following suction D&C, a repeat D&C may be a harmful option compared to direct hysteroscopic resection because of the increased risk of intrauterine adhesions.

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**REFERENCES**