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OBG MANAGEMENT

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PELVIC FLOOR DYSFUNCTION UPDATE

Universal cystoscopy? The evidence is stacking

Surgical technique: Myomectomy of a large cervical fibroid

AVOIDING OBSTETRIC EMERGENCIES

How to detect placenta accreta with prenatal ultrasound

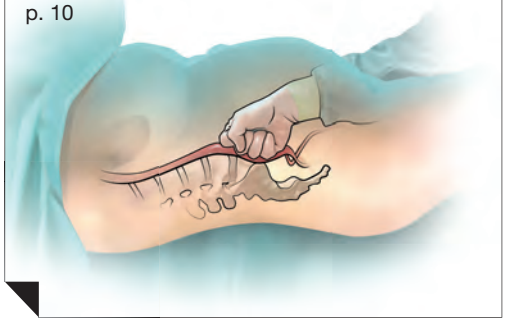
Jennifer Philips, MD;
Alfred Abuhamad, MD

SCOTUS: Term recap, and clues to the future

Failure to respond to hemorrhage alerts, more Medical Verdicts

Aortic compression to reduce PPH

p. 10



NOW APPROVED—

For the first time in over a decade, a new oral treatment option for the management of moderate to severe pain associated with endometriosis.

rilissa™
elagolix tablets 150 mg 200 mg

- Available in 2 oral dosages (150 mg QD and 200 mg BID)[1]

The first and only oral GnRH antagonist specifically developed for women with moderate to severe endometriosis pain[1]

Dysmenorrhea
(150 mg or 200 mg)

Nonmenstrual Pelvic Pain
(150 mg or 200 mg)

Dyspareunia*
(200 mg only)

*Statistical significance for dyspareunia was not achieved with the 150-mg dose of ORILISSA.[1]

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Bone Loss

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

- Women who take ORILISSA may experience a reduction in the amount, intensity, or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

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

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

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

ADVERSE REACTIONS

- The most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes.

These are not all the possible side effects of ORILISSA.

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

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

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

Learn more about this new treatment option at ORILISSA.com/hcp

NEW Orilissa™ elagolix tablets 150 mg 200 mg

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 400-1939046 Printed in the U.S.A. July 2018

ORILISSA™ (elagolix) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Important Dosing Information

- Exclude pregnancy before starting ORILISSA or start ORILISSA within 7 days from the onset of menses.
- Take ORILISSA at approximately the same time each day, with or without food.
- Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives *[see Warnings and Precautions]*.
- Limit the duration of use because of bone loss (Table 1) *[see Warnings and Precautions]*.

Table 1. Recommended Dosage and Duration of Use

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

Hepatic Impairment

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

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

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

Missed Dose

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

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

CONTRAINDICATIONS

ORILISSA is contraindicated in women:

- Who are pregnant *[see Use in Specific Populations]*. Exposure to ORILISSA early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis because of the risk of further bone loss *[see Warnings and Precautions]*
- With severe hepatic impairment because of the risk of bone loss *[see Use in Specific Populations]*
- With concomitant use of strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil) *[see Drug Interactions]*

WARNINGS AND PRECAUTIONS

Bone Loss

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

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

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Women who take ORILISSA may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner *[see Adverse Reactions]*. Perform pregnancy testing if pregnancy is suspected, and discontinue ORILISSA if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ORILISSA in the endometriosis clinical trials. ORILISSA subjects had a higher incidence of depression and mood changes compared to placebo, and ORILISSA subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history *[see Adverse Reactions]*. Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits *[see Adverse Reactions]*. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing ORILISSA if such events occur.

Hepatic Transaminase Elevations

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

Reduced Efficacy with Estrogen-Containing Contraceptives

Based on the mechanism of action of ORILISSA, estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA. The effect of progestin-only contraceptives on the efficacy of ORILISSA is unknown. Advise women to use non-hormonal contraceptives during treatment with ORILISSA and for one week after discontinuing ORILISSA *[see Use in Specific Populations, Drug Interactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

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

Clinical Trials Experience

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

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

Serious Adverse Events

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

Adverse Reactions Leading to Study Discontinuation

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

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

Common Adverse Reactions:

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

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

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

Less Common Adverse Reactions:

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

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

Bone Loss

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

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

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

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

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

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

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

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

Figure 1. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 6 Months off Therapy in Studies EM-2/EM-4

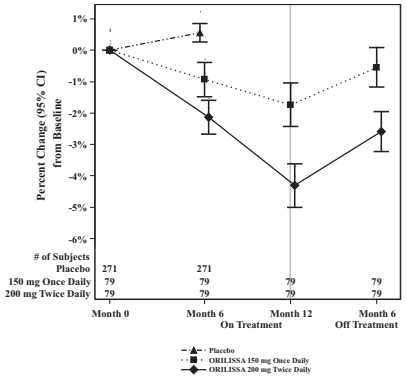
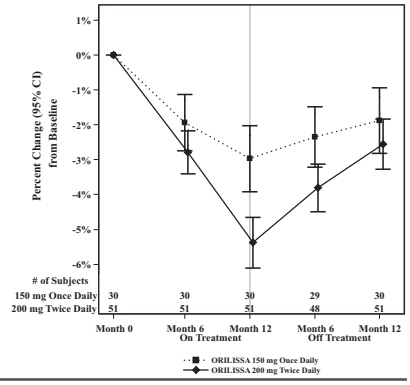


Figure 2. Percent Change from Baseline in Lumbar Spine BMD in Subjects Who Received 12 Months of ORILISSA and Had Follow-up BMD 12 Months off Therapy in Studies EM-2/EM-4



Suicidal Ideation, Suicidal Behavior and Exacerbation of Mood Disorders

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

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

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

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

Among the 2090 subjects exposed to ORILISSA in the endometriosis Phase 2 and Phase 3 studies, there were four reports of suicidal ideation. In addition to the two subjects in Table 4, there were two additional reports of suicidal ideation: one subject in EM-3 (150 mg once daily) and one in a Phase 2 study (75 mg once daily, an unapproved dose). Three of these subjects had a history of depression. Two subjects discontinued ORILISSA and two completed the clinical trial treatment periods.

Hepatic Transaminase Elevations

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

Changes in Lipid Parameters

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

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

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

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

Hypersensitivity Reactions

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

Endometrial Effects

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

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

Effects on menstrual bleeding patterns

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

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

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

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

ORILISSA also demonstrated a dose-dependent increase in the percentage of women with amenorrhea (defined as no bleeding or spotting in a 56-day interval) over the treatment period. The incidence of amenorrhea during the first six months of treatment ranged from 6-17% for ORILISSA 150 mg once daily, 13-52% for ORILISSA 200 mg twice daily and less than 1% for placebo. During the second 6 months of treatment, the incidence of amenorrhea ranged from 11-15% for ORILISSA 150 mg once daily and 46-57% for ORILISSA 200 mg twice daily.

After 6 months of therapy with ORILISSA 150 mg once daily, resumption of menses after stopping treatment was reported by 59%, 87% and 95% of women within 1, 2, and 6 months, respectively. After 6 months of therapy with ORILISSA 200 mg twice daily, resumption of menses after stopping treatment was reported by 60%, 88%, and 97% of women within 1, 2, and 6 months, respectively.

After 12 months of therapy with ORILISSA 150 mg once daily resumption of menses after stopping treatment was reported by 77%, 95% and 98% of women within 1, 2, and 6 months respectively. After 12 months of therapy with ORILISSA 200 mg twice daily resumption of menses after stopping treatment was reported by 55%, 91% and 96% of women within 1, 2, and 6 months respectively.

DRUG INTERACTIONS

Potential for ORILISSA to Affect Other Drugs

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

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

Potential for Other Drugs to Affect ORILISSA

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

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

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

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

Drug Interactions - Examples and Clinical Management

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

Table 7. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Elagolix or Concomitant Drug	Clinical Recommendations
Antiarrhythmics digoxin	↑ digoxin	Clinical monitoring is recommended for digoxin when co-administered with ORILISSA.
Antimycobacteria rifampin	↑ elagolix	Concomitant use of ORILISSA 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ORILISSA 150 mg once daily and rifampin to 6 months.
Benzodiazepines oral midazolam	↓ midazolam	Consider increasing the dose of midazolam and individualize therapy based on the patient's response.
Statins rosuvastatin	↓ rosuvastatin	Consider increasing the dose of rosuvastatin.

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

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

Data

Human Data

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

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

Animal Data

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

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

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

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

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

Lactation

Risk Summary

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

Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Renal Impairment

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

Hepatic Impairment

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (12 to 13-fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans.

Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay.

In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat *[see Use in Specific Populations]*, and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

- Advise patients on contraceptive options, not to get pregnant while using ORILISSA, to be mindful that menstrual changes could reflect pregnancy and to discontinue ORILISSA if pregnancy occurs *[see Contraindications and Warnings and Precautions]*.
- Inform patients that estrogen containing contraceptives are expected to reduce the efficacy of ORILISSA.
- Inform patients about the risk of bone loss. Advise adequate intake of calcium and vitamin D *[see Warnings and Precautions]*.
- Advise patients to seek immediate medical attention for suicidal ideation and behavior. Instruct patients with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions]*.
- Counsel patients on signs and symptoms of liver injury *[see Warnings and Precautions]*.
- Instruct patients who miss a dose of ORILISSA to take the missed dose on the same day as soon as she remembers and then resume the regular dosing schedule:
  - 150 mg once daily: no more than 1 tablet each day should be taken.
  - 200 mg twice daily: no more than 2 tablets each day should be taken.
- Instruct patients to dispose of unused medication via a take-back option if available or to otherwise follow FDA instructions for disposing of medication in the household trash, www.fda.gov/drugdisposal, and not to flush down the toilet.

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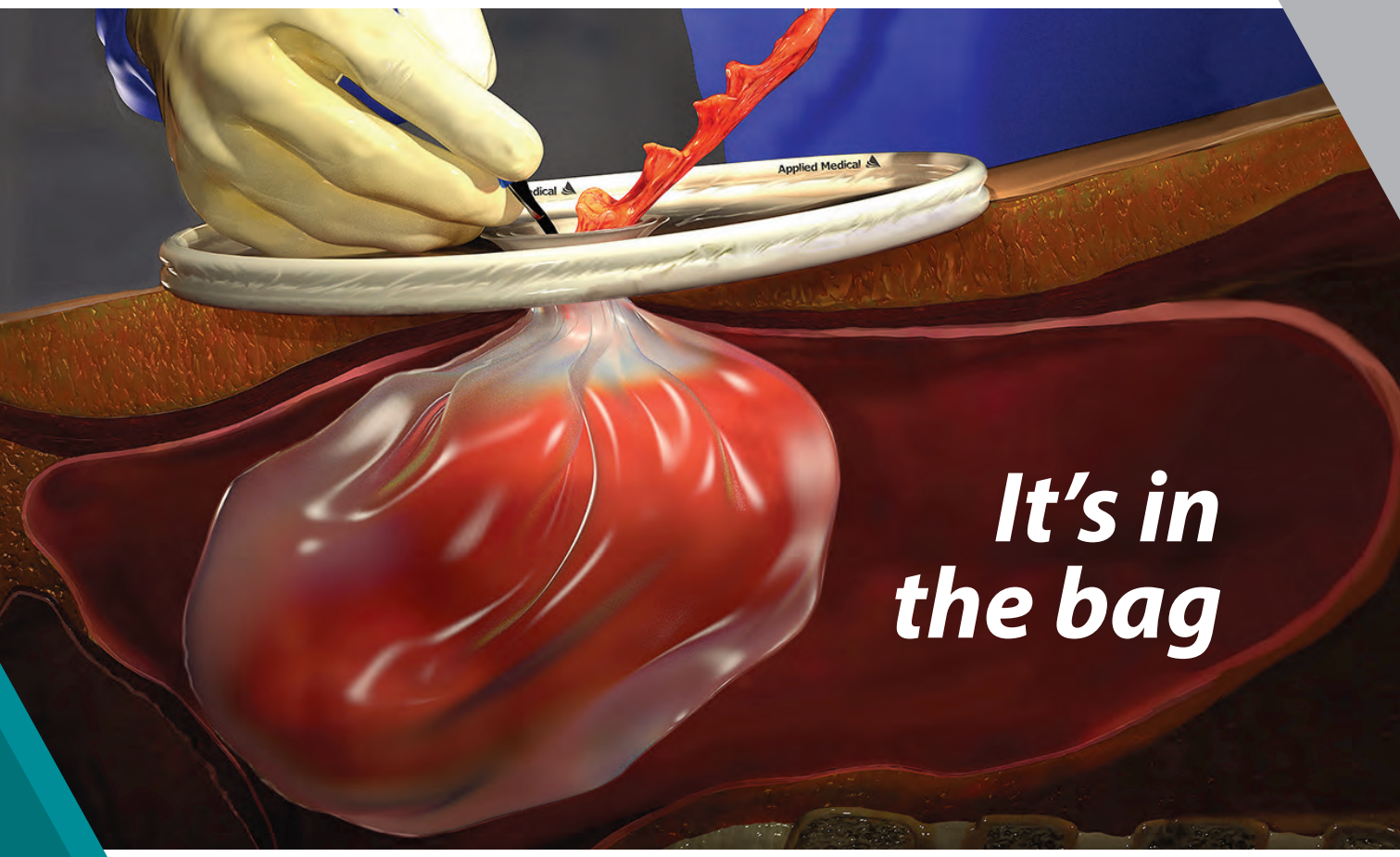

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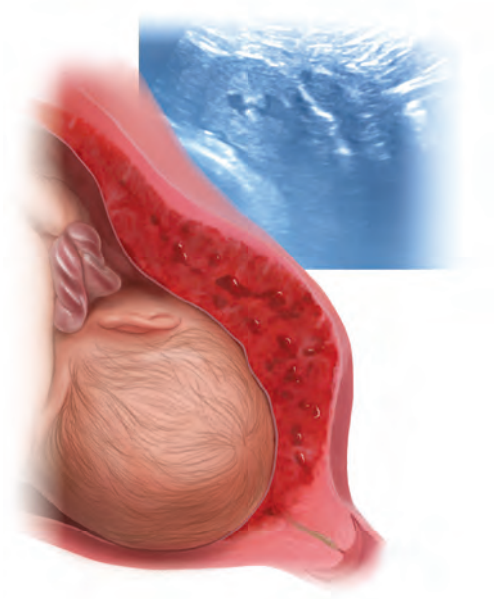

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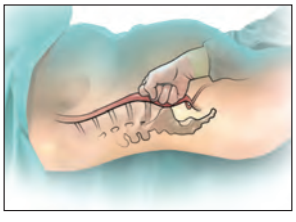
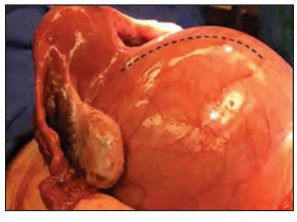


Aortic compression **10**



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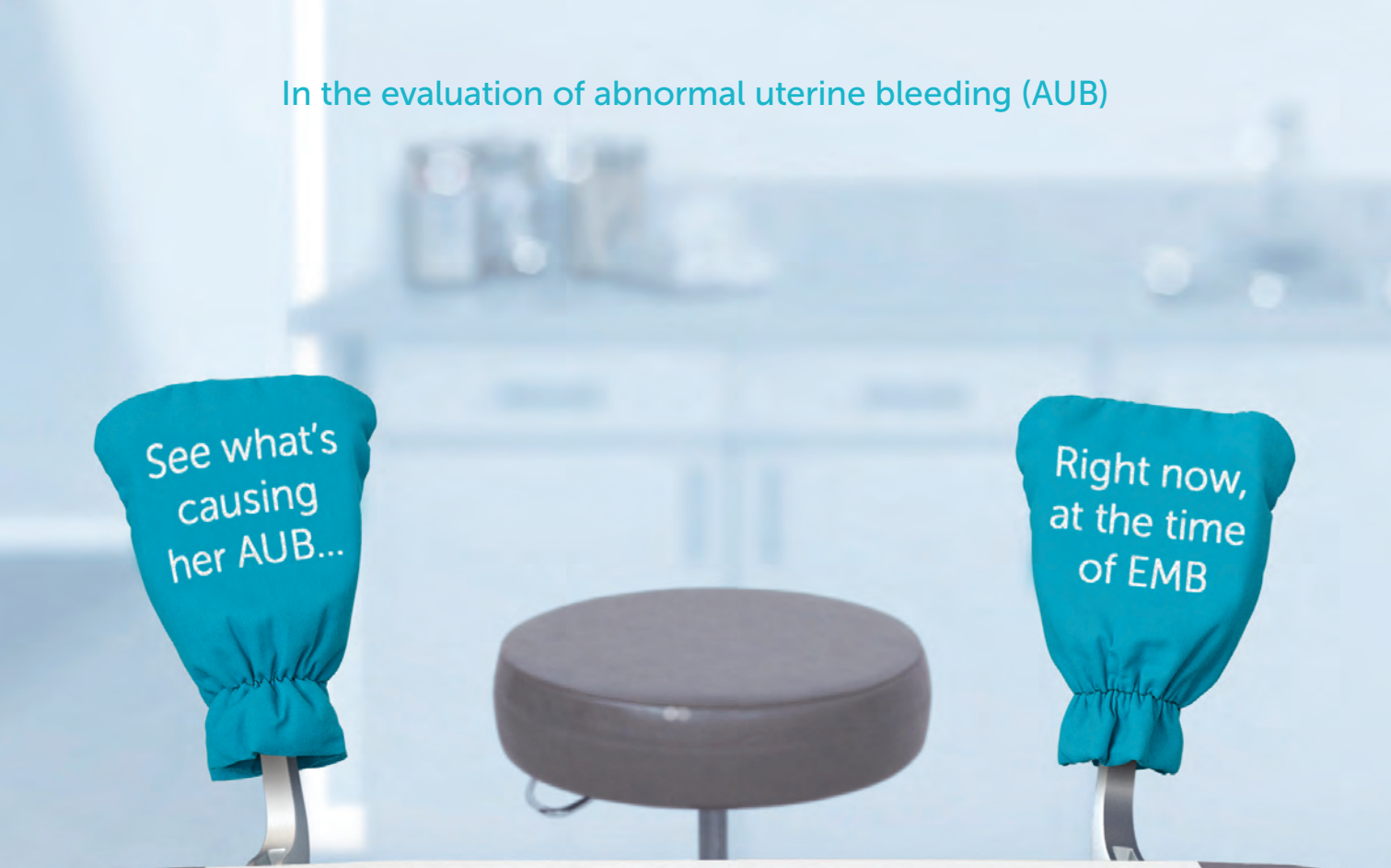

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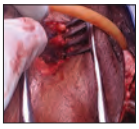

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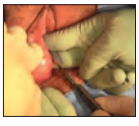

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EDITORIAL

Postpartum hemorrhage: Aortic compression to reduce pelvic bleeding

Although aortic compression generally is not taught to obstetricians as a maneuver to control major pelvic hemorrhage, anesthesiologists are aware of its value and may ask you to initiate this maneuver in the setting of severe postpartum hemorrhage

Robert L. Barbieri, MD
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Chair, Obstetrics and Gynecology
Brigham and Women's Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School, Boston

You are performing a repeat cesarean delivery on a 37-year-old G3P2 woman with placenta previa. Immediately after delivery, a postpartum hemorrhage occurs. You order additional uterotonic medications and blood products and prepare for standard surgical interventions including uterine devascularization, uterine compression sutures, and intrauterine balloon tamponade. As the hemorrhage continues, you begin to consider the need to perform a hysterectomy.

Instant Poll

What is your best approach to treating a severe case of postpartum hemorrhage?

Tell us at rbarbieri@mdedge.com
Please include your name and city and state.

Suddenly the anesthesiologist reports that the patient's blood pressure and heart rate have decreased. She asks you to initiate aortic compression to slow the pelvic bleeding and permit initiation of interventions to restore intravascular volume and optimize cardiovascular status. You have not previously performed this maneuver, and you wonder how to respond to her request.

Preoperative preparation

Anticipating possible adverse outcomes is a key task for every clinician. In the above case, in the setting of a repeat cesarean delivery in a woman with placenta previa, there is an increased risk of postpartum hemorrhage. Therefore, appropriate blood products and equipment should be made available before the operation is initiated. It also may be helpful to review the sequential steps you have found most useful in managing a postpartum hemorrhage prior to starting the procedure.

Rapid response to obstetric hemorrhage

When postpartum hemorrhage occurs during a cesarean delivery, there are many interventions that may successfully control the excessive blood loss, including uterotonics, massive transfusion of blood products, uterine massage, tranexamic acid, uterine devascularization, uterine compression sutures, intrauterine balloon tamponade, uterine artery embolization, uterine tourniquet, internal iliac artery ligation, hysterectomy, and pelvic packing.[1] Rapid response to obstetric hemorrhage is important to avoid depletion of coagulation factors and subsequent development of a coagulation disorder. Once a coagulation disorder occurs, it can be very difficult to resolve the problem and complete the surgery.

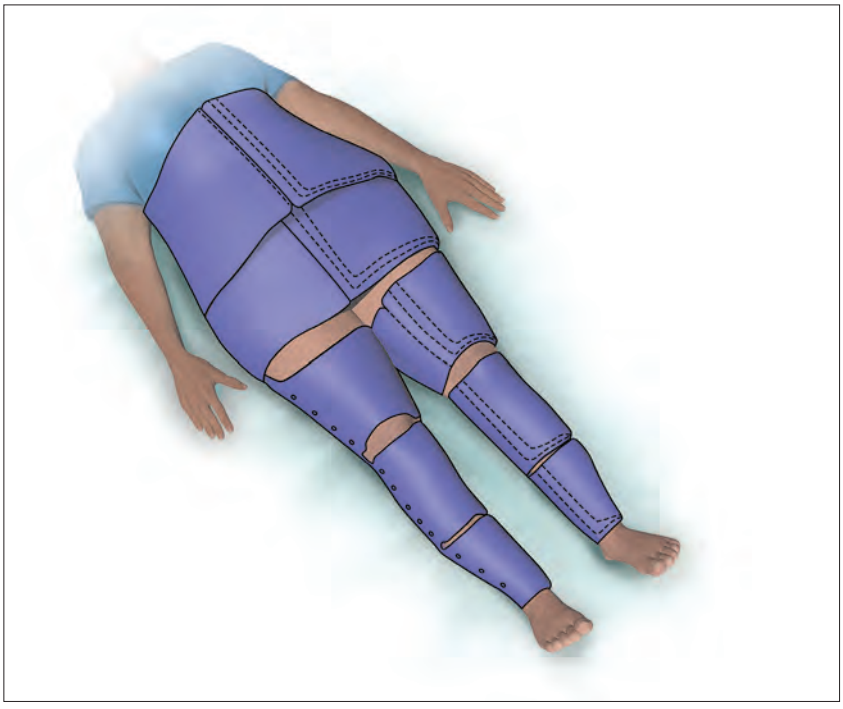
Abdominal compression

The potentially benefial role of abdominal compression to help

reduce blood loss caused by trauma or obstetric hemorrhage has been studied extensively in healthy volunteers. The theory is that abdominal compression will decrease blood flow in the distal aorta, helping to control bleeding in the pelvis and extremities. In one report, 80 to 140 lb of pressure applied to the epigastrium in 9 healthy male participants in a supine position on a rigid surface resulted in decreased blood flow in the common femoral artery as determined by pulsed-wave Doppler ultrasound.[2] Abdominal pressure applied above the umbilicus also has been reported to reduce blood pressure in the legs.[3] Abdominal compression and tourniquets used on the extremities are not meant to be definitive treatments for traumatic hemorrhages but rather are used to stabilize severely injured patients during transport to emergency surgical care facilities.[4]

One approach to performing manual abdominal aortic compression involves first gaining a mechanical advantage by positioning yourself above the epigastric area with arms extended. Using one closed fist with the opposite hand providing additional pressure, the equivalent of 80 to 140 lb can be applied to the patient's upper abdomen.[4] To estimate the pressure you can achieve using this method, cover a scale with a towel and use your arms to exert maximum pressure on the scale. What equivalent weight can you reach when applying maximum pressure? What weight can you sustain for a few minutes? Using manual compression, it is difficult for a clinician to exert the equivalent of 140 lb on the epigastrium for the extended period of time needed to transport an injured person to an emergency facility.[5] Therefore, mechanical devices such as the abdominal aortic tourniquet (AAT) and the nonpneumatic antishock garment (NASG) have been developed to aid in providing continuous abdominal compression.

FIGURE 1 Nonpneumatic antishock garment



The neoprene device's panels reduce blood flow to the pelvis and extremities

Abdominal aortic tourniquet. The AAT is a corset-like device with an interior pneumatic bladder that is designed to provide sustained compression over the abdomen, therefore compressing the abdominal aorta and reducing blood flow to the pelvis and extremities. In one study with human volunteers, a median pressure of 180 mm Hg (range, 150–230 mm Hg) was associated with cessation of blood flow in the common femoral artery in 7 of 9 volunteers and a decrease in blood flow in all participants as determined by pulsed-wave Doppler ultrasound.[6] Participants reported moderate to severe discomfort when the AAT was inflated to a pressure sufficient to stop blood flow in the femoral artery. The AAT device may not be as effective in individuals with an elevated body mass index and excessive abdominal girth.[7] In obstetric postpartum hemorrhage, abdominal pressure also has been reported to reduce hemorrhage and femoral artery blood flow. Using a corset-like abdominal binder with an internal spring to provide continuous pressure over the anterior abdomen, Soltan and Sadek reported a beneficial effect of abdominal pressure in the management of severe postpartum hemorrhage in a large observational study in Egypt.[8,9]

Nonpneumatic antishock garment. The NASG has been studied extensively as a method to help safely transport a woman with severe postpartum hemorrhage to an emergency

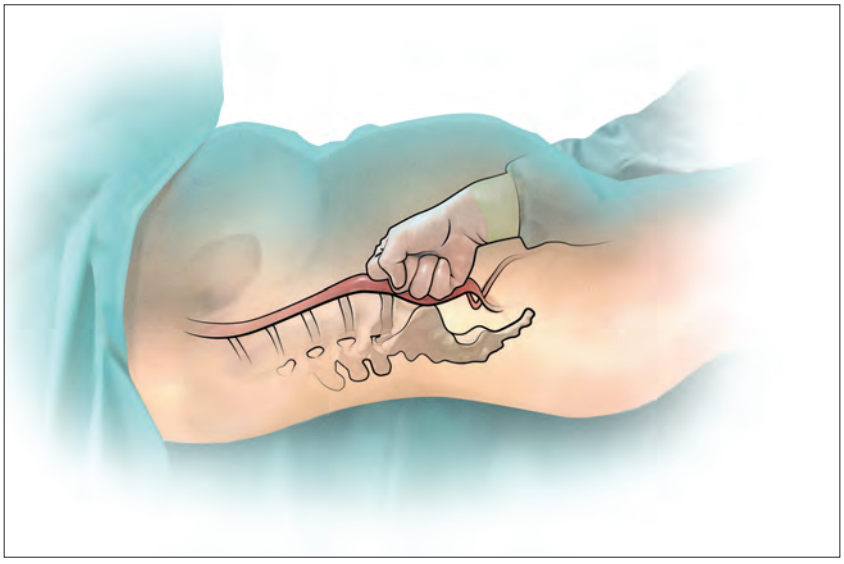
facility. The NASG is a neoprene and Velcro device with panels for the lower extremities, pelvis, and abdomen (**FIGURE 1,** page 11). The device also has an abdominal segment that includes a compression ball to provide continuous abdominal pressure. When the panels are closed, blood flow to the extremities and pelvis is reduced. In a study of 10 postpartum volunteers, application of the NASG caused decreased blood flow in the internal iliac artery as measured by Doppler ultrasound, but blood flow did not stop completely.[10] In an observational study of women with postpartum hemorrhage, use of the NASG device in combination with usual interventions resulted in a decrease in blood loss.[11]

In a cluster randomized trial, 38 birth centers in Africa were randomly assigned to standard management of obstetric hemorrhage or the same protocol plus use of the NASG prior to transport to a regional emergency surgical center. Compared with the group receiving standard management alone, the women who received standard management plus the NASG device had a nonsignificant reduction in maternal mortality (odds ratio, 0.54; 95% confidence interval [CI], 0.14–2.05; $P = .37$) and a significantly more rapid recovery from hypovolemic shock (hazard ratio, 1.25; 95% CI, 1.02–1.52; $P = .03$).[12] The International Federation of Gynecology and Obstetrics has issued a guideline supporting the use of the device in the management of obstetric hemorrhage in appropriate settings.[13]

Aortic compression in the setting of an open abdominal incision

During cesarean delivery, the surgeon has access to the abdominal aorta via the open abdominal incision and can directly apply pressure to the aorta at sites ranging from above the sacral promontory to the subdiaphragmatic aorta. Although aortic compression is occasionally noted as a potential intervention to help with the management of postpartum hemorrhage, there is very little literature on this intervention.[1] In one case report of an emergency laparotomy in a Jehovah's Witness patient with a placenta previa, uterine rupture, massive hemorrhage (hematocrit nadir of 6%), and hypovolemic shock, direct pressure applied to the infradiaphragmatic aorta and pelvic organs permitted the anesthesiologist to stabilize the patient's cardiovascular status, facilitating the patient's recovery from shock.[14] The authors of the case concluded that compression of the aorta and pelvic organs can be lifesaving and is underutilized in the management of uncontrolled obstetric hemorrhage. Other case reports also recommend considering the use of aortic compression to permit the anesthesia team to resuscitate a bleeding patient.[15]

FIGURE 2 Aortic compression through an open abdominal incision



During cesarean delivery through a low transverse abdominal incision, the surgeon directly applies pressure to the aorta just above the lumbosacral promontory

There is very little published guidance on how to perform aortic compression at cesarean delivery. Techniques for aortic compression include using a closed fist or the heel of the hand to compress the aorta against the lumbosacral spine. Alternatively, use a moist rolled-up surgical towel or laparotomy sponge to compress the aorta against the lumbosacral spine. With a low transverse abdominal incision, the aorta just above the lumbosacral promontory is closest to the surgeon (aorta zone III) (**FIGURE 2**). If a vertical abdominal incision has been made, the subdiaphragmatic aorta may be within reach of the surgeon (aorta zone II). If an anesthesiologist asks you to apply aortic compression, it is likely that the patient is hypotensive. In this setting, reducing blood flow through the aorta can be achieved

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with less pressure than required for successful aortic compression in a healthy volunteer.

Prolonged aortic compression that completely obstructs blood flow may result in downstream ischemia. This is illustrated by leg ischemia and amputation that have occurred following the use of the resuscitative endovascular balloon occlusion of the aorta (REBOA) occlusion device.[16] Another strategy that has been used in the management of massive hemorrhage, when immediate replacement of clotting factors is not possible, is damage control surgery, a technique in which capillary and venous bleeding is controlled by placing pelvic packs or a pelvic umbrella pressure pack and sending the patient to the intensive care unit for resuscitation.[17] With damage control surgery, a second procedure is planned to remove the packs after the patient has been stabilized.

With knowledge and practice comes preparedness

Hopefully you will never be asked by an anesthesiologist to stop operating and initiate aortic compression. With effective preprocedure preparation and rapid institution of standard postpartum hemorrhage techniques, it is unlikely aortic compression ever will be needed. If an unusually difficult case triggers a request for aortic compression, you have the knowledge and skills to provide that service. ●

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

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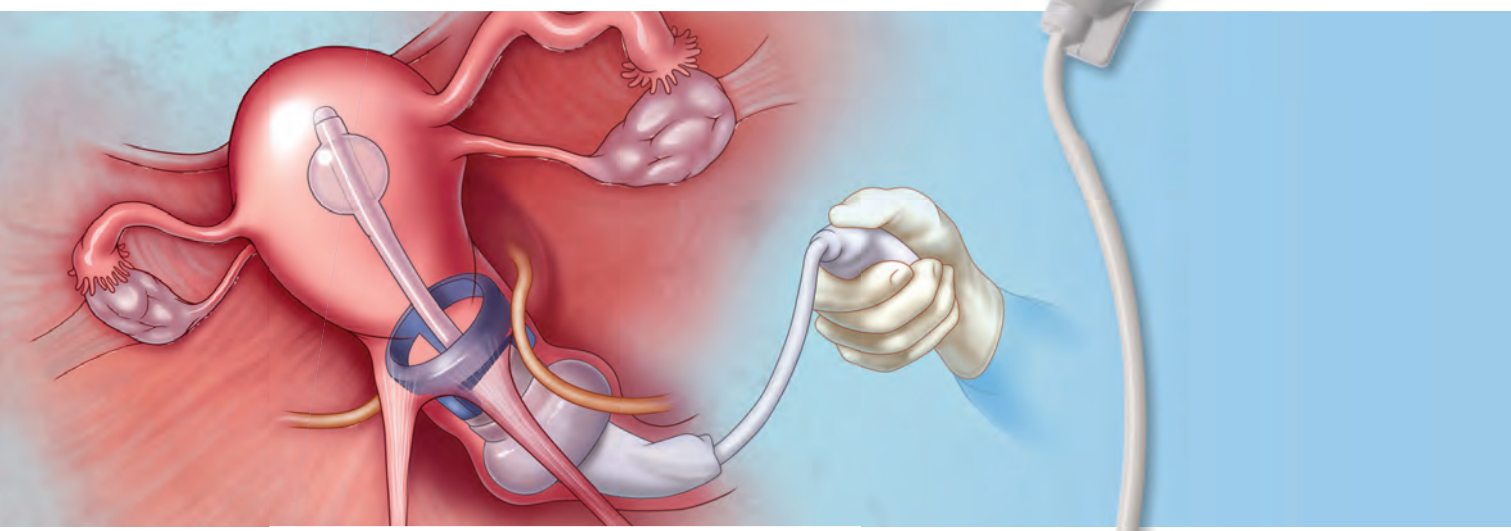

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ARE WE READY FOR PRIMARY HPV TESTING FOR THE PREVENTION OF CERVICAL CANCER?
SARAH FELDMAN, MD, MPH; ROBERT L. BARBIERI, MD
(EDITORIAL; JULY 2018)

Multiple payment systems impede universal HPV screening access

Unless the issue of multiple systems of payment and access (that is, multiple insurance companies and providers) can be resolved in the United States, I do not believe there will be an advancement across the board for human papillomavirus (HPV) screening. In my opinion, we need to work toward access to health care for all and a single-payer system.

C.L. Conrad-Forrest, MD
Davis, California

Dr. Barbieri responds

I agree with Dr. Conrad-Forrest that improving cervical cancer screening would be advanced by interoperable electronic medical records and health systems that are designed to manage population health. I predict that a large integrated health system will be the first to adopt the use of high-risk HPV testing to screen for cervical cancer in the United States.

VIDEO: SIZE CAN MATTER: LAPAROSCOPIC HYSTERECTOMY FOR THE VERY LARGE UTERUS
DEIRDRE LUM, MD
(SOCIETY OF GYNECOLOGIC SURGEONS; JULY 2018)

Laparoscopic suturing is an option

Dr. Lum presented a nicely produced video demonstrating various strategies aimed at facilitating total laparoscopic hysterectomy (TLH) of the very large uterus (www.mdedge.com/obgyn/article/168309/surgery/size-can-matter-laparoscopic-hysterectomy-very-large-uterus).

JULY 2018

Her patient's evaluation included magnetic resonance imaging. In the video, she demonstrates a variety of interventions, including the use of a preoperative gonadotropin–releasing hormone (GNRH) agonist and immediate perioperative radial artery–uterine artery embolization. Intraoperative techniques include use of ureteral stents and securing the uterine arteries at their origins.

Clearly, TLH of a huge uterus is a technical challenge. However, I'd like to suggest that a relatively basic and important skill would greatly assist in such procedures and likely obviate the need for a GNRH agonist and/or uterine artery embolization. The vessel-sealing devices shown in the video are generally not capable of sealing such large vessels adequately, and this is what leads to the massive hemorrhaging that often occurs.

Laparoscopic suturing with extracorporeal knot tying can be used effectively to control the extremely large vessels associated with a huge uterus. The judicious placement of sutures can completely control such vessels and prevent bleeding from both proximal and distal ends when 2 sutures are placed and the vessels are transected between the stitches. Many laparoscopic surgeons have come to rely on bipolar energy or ultrasonic devices to coagulate vessels. But when dealing with huge vessels, a return to basics using laparoscopic suturing will greatly benefit the patient and the surgeon by reducing blood loss and operative time.

David L. Zisow, MD
Baltimore, Maryland

Dr. Lum responds

I thank Dr. Zisow for his thoughtful comments. I agree that laparoscopic suturing is an essential skill that can be utilized to suture ligate vessels. If we consider the basics of an open hysterectomy, the uterine artery is clamped first, then suture ligated. When approaching a very large vessel during TLH, I would be concerned that a simple suture around a large vessel might tear through and cause more bleeding. To mitigate this risk, the vessel can be clamped with a grasper first, similar to the approach in an open hysterectomy. However, once a vessel is compressed, a sealing device can usually work just as well as a suture. It becomes a matter of preference and cost.

During hysterectomy of a very large uterus, a big challenge is managing bleeding of the uterus itself during manipulation from above. Bleeding from the vascular sinuses of the myometrium can be brisk and obscure visualization, potentially leading to laparotomy conversion. A common misconception is that uterine artery embolization is equivalent to suturing the uterine arteries. In actuality, the goal of a uterine artery embolization is to embolize the distal branches of the uterine arteries, which can help with any potential bleeding from the uterus itself during hysterectomy.

CONTINUED ON PAGE 17

2018

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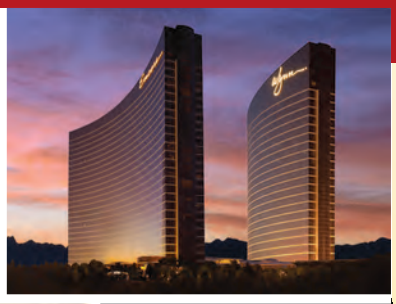


COURSE CHAIRS

Tommaso Falcone, MD
Cleveland Clinic London

Mickey M. Karram, MD
The Christ Hospital

SPECIAL KEYNOTE SPEAKER

Sawsan As-Sanie, MD, MPH
University of Michigan

Faculty

Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
Cleveland Clinic

Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
Johns Hopkins Hospital

John B. Gebhart, MD, MS
Mayo Clinic

Rosanne M. Kho, MD
Cleveland Clinic

Javier F. Magrina, MD
Mayo Clinic Phoenix

Beri M. Ridgeway, MD
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- Tissue Extraction Techniques
- Laparoscopic Suturing
- Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
- Office-Based Gynecologic Procedures

SPECIAL KEYNOTES

- Management of Chronic Pelvic Pain
- Non-Opioid Pain Management after Minimally Invasive Hysterectomy

PLUS

- Hysterectomy Techniques
  Vaginal • Single Port • Robotic • Total Laparoscopic • Morcellation • Preserving Level 1 Support • When is it Appropriate to Remove the Ovaries?
- Incontinence and Prolapse Surgery
- Avoiding and Managing Complications
- Gynecologic Oncology for the Generalist
- Medical Legal Cases
- Fibroid Management
- Surgical Tips for Successful Pelvic Surgery Video Session
- Non-Surgical Management of Incontinence and Pelvic Floor Disorders

AND, Optional Post-Conference P.E.P. Practice Management Workshop

To register and for complete information please see our website: **PAGS-cme.org**.

PAGS AGENDA

Agenda and faculty is subject to change. Please see website for updates.

TUESDAY, DECEMBER 4, 2018

Optional Opioid REMS Course NEW!
Optional, free course. Pre-registration required
Pain Management and Opioids: Balancing Risks and Benefits
3:00 PM - 6:15 PM

WEDNESDAY, DECEMBER 5, 2018

Optional Hands-On Workshops

Tissue Extraction Techniques
8:30 AM–12:30 PM

Laparoscopic Suturing - The "Vertical Zone"
8:30 AM–12:30 PM

Office-Based Gynecologic Procedures
8:30 AM–5:30 PM

Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
1:30 PM–5:30 PM

THURSDAY, DECEMBER 6, 2018

6:30 AM **Registration/Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

7:55 AM **Course Overview**
Mickey M. Karram, MD

PELVIC ANATOMY

8:00 AM **Pelvic and Abdominal Anatomy from the Laparoscopic Surgeon's View**
Tommaso Falcone, MD

8:40 AM **Anatomic Considerations: Facilitating Vaginal Procedures Safely and Effectively**
Mickey M. Karram, MD

INCONTINENCE AND PROLAPSE SURGERY

9:10 AM **Panel Discussion: Evaluation and Non-Surgical Management of Female Pelvic Floor Disorders: What Every Generalist Should Know**
John B. Gebhart, MD, MS
Mickey M. Karram, MD
Beri M. Ridgeway, MD

9:55 AM **Question and Answer Session**

10:25 AM **Break/Exhibits**

11:10 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

11:40 AM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD, MS

12:10 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:40 PM **Question and Answer Session**

1:10 PM **Luncheon Symposium**

2:10 PM **Dessert Break/ Exhibits**

THURSDAY'S KEYNOTE LECTURE

2:40 PM **Management of Chronic Pelvic Pain in Women**
Sawsan As-Sanie, MD, MPH

FIBROID MANAGEMENT & PRINCIPLES OF ELECTROSURGERY

3:25 PM **Safe Use of Energy-Based Devices for Gynecologic Surgery**
Andrew I. Brill, MD

3:55PM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

4:25 PM **Break/Exhibits**

4:40 PM **The Hysteroscopic Treatment of Submucosal Fibroids and Polyps**
Linda D. Bradley, MD

5:10 PM **Question and Answer Session**

FRIDAY, DECEMBER 7, 2018

7:00 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

8:15 AM **The Difficult Vaginal Hysterectomy**
Rosanne M. Kho, MD

8:50 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:25 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

10:00 AM **Break /Exhibits**

10:45 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:15 AM **Tissue Extraction Techniques (Morcellation)**
Tommaso Falcone, MD

11:45 AM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Beri M. Ridgeway, MD

12:15 PM **Which Hysterectomy Approach is Best?**
Case Presentation and
Audience Participation – all speakers

12:45 PM **Question and Answer Session**

1:00 PM **Luncheon Symposium**

2:00 PM **Dessert Break/Exhibits**

FRIDAY'S KEYNOTE LECTURE

2:30 PM **Non-Opioid Pain Management after Minimally Invasive Hysterectomy**
Sawsan As-Sanie, MD, MPH

ONCOLOGY FOR THE GENERALIST

3:15 PM **Surgical Management of Pre-Cancer Vulvovaginal Lesions**
Amanda Nickles Fader, MD

4:00 PM **Laparoscopic and Robotic Management of the Adnexal Mass**
Javier F. Magrina, MD

4:45 PM **Spectrum of Vulvovaginal Disorders**
Michael S. Baggish, MD

5:30 PM **Question and Answer Session**

SATURDAY, DECEMBER 8, 2018

6:30 AM **Breakfast**

7:30 AM **Management of Endometriosis**
Tommaso Falcone, MD

8:30 AM **Avoiding and Managing Urogynecologic Complications**
John B. Gebhart, MD, MS
Mickey M. Karram, MD

9:30 AM **Avoiding and Managing Laparoscopic Complications**
Tommaso Falcone, MD

10:30 AM **Break**

10:45 AM **Medical Legal Cases**
Michael S. Baggish, MD
Tommaso Falcone, MD

11:30 AM **Surgical Tips for Successful Pelvic Surgery: Video Session**
Surgical Management of Cornual Ectopic & Dermoid Cysts
Tommaso Falcone, MD

Techniques to Suspend the Apex at the Time of Vaginal Surgery
Mickey M. Karram, MD

1:00 PM **PAGS Scientific Program Adjournment**

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P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional)

Make Your Practice More Profitable, Efficient, and Productive!

Director
Neil H. Baum, MD
Former Associate Clinical Professor of Urology
Tulane Medical School
Louisiana State University
New Orleans, Louisiana

Dr. Neil Baum is the author of *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

SATURDAY, DECEMBER 8, 2018

2:00 PM **Course Overview**

2:10 PM **Looking at the 4 Pillars of a Successful Practice in the Current Healthcare Environment**
- The 4 Pillars of a Successful Practice
- How to Improve the Efficiency, Productivity, and Profitability of Your Practice
- Online Reputation Management
- Why Market and Promote Your ObGyn Practice

3:30 PM **Break**

3:45 PM
- Using Social Media to Get to the Top of Google
- Numbers You Need to Know
- Moving from Volume to Value

5:00 PM **Q and A**

5:30 PM **P.E.P. Adjournment**

PAGS Scientific Faculty

Course Chairs

Tommaso Falcone, MD
Chief of Staff
Chief Academic Officer
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Cleveland, Ohio

Mickey M. Karram, MD
Director of Urogynecology
The Christ Hospital
Volunteer Professor of OB/GYN
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Sawsan As-Sanie, MD, MPH
Director
Minimally Invasive Gyn Surgery and Chronic Pelvic Pain
University of Michigan
Ann Arbor, Michigan

Faculty

Michael S. Baggish, MD
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St. Helena Hospital
St. Helena, California

Linda D. Bradley, MD
Vice Chair
Obstetrics, Gynecology, and Women's Health Institute
Director
Center for Menstrual Disorders
Professor of Surgery
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Andrew I. Brill, MD
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California Pacific Medical Center
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Amanda Nickles Fader, MD
Associate Professor and Director
Kelly Gynecologic Oncology Service
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Director
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Barbara Woodward Lips Professor
Mayo Clinic
Phoenix, Arizona

Beri M. Ridgeway, MD
Department Chair, Regional Ob/Gyn
Cleveland Clinic
Assistant Professor
Cleveland Clinic Learner College of Medicine
Cleveland, Ohio

Optional Workshops

For complete information please see PAGS-CME.org.

Tuesday, December 4, 2018, Encore at Wynn Las Vegas

Optional Opioid REMS Course *Free to PAGS attendees*

OPIOID RISK EVALUATION AND MITIGATION STRATEGIES (REMS) COURSE "PAIN MANAGEMENT AND OPIOIDS: BALANCING RISKS AND BENEFITS"
3.0 CME/CNE Credits Available
3:00 PM - 6:15 PM Pre-registration required. See PAGS website for complete details.

Wednesday, December 5, 2018, Encore at Wynn Las Vegas

Optional Hands-on Workshops

PAGS hands-on workshops have limited space available and will sell out. First come. First served! **(See PAGS website for complete details.)**

WORKSHOP A
TISSUE EXTRACTION TECHNIQUES
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Rosanne M. Kho, MD
Faculty: Andrew I. Brill, MD; Keith B. Isaacson, MD

WORKSHOP B
HANDS-ON LAPAROSCOPIC SUTURING - THE "VERTICAL ZONE" (SIMULATION LAB)
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Charles H. Koh, MD

WORKSHOP C
OFFICE-BASED GYNECOLOGIC PROCEDURES: THE GYNECOLOGIST OF THE FUTURE NEW!
FULL-DAY WORKSHOP
8 CME Credits Available
8:30 AM - 5:30 PM
Includes a morning lecture series and afternoon practicum on vulvar/vaginal injections and excisions, ultrasound and hysteroscopy

Led by: Tommaso Falcone, MD
Faculty: Andrew Brill, MD; Linda D. Bradley, MD; Mark Dassel, MD; Laura Detti, MD; Oluwatosin Goje, MD; Keith Isaacson, MD; Mickey Karram, MD; James M. Shwayder, MD, JD

WORKSHOP D
TECHNICAL ASPECTS OF VAGINAL HYSTERECTOMY & CYSTOURETHROSCOPY FOR THE GYNECOLOGIST
4 CME Credits Available
1:30 PM - 5:30 PM
Led by: Mickey Karram, MD
Faculty: Rosanne M. Kho, MD; Doug Miyazaki, MD

Who Should Attend?

The PAGS conference is designed for obstetricians/gynecologists, second, third and fourth-year residents in OB/GYN, as well as sub-specialty fellows and advanced practice clinicians. Residents and advanced practice health clinicians are welcome at reduced rates.

ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Global Academy for Medical Education, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

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Optional **"P.E.P." PRACTICE MANAGEMENT PROGRAM**
3.25 CME Credits Available
December 8, 2018

About Our Venue Encore at Wynn Las Vegas

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Discount room rate expires November 6, but we urge you to make your arrangements as soon as possible as our room block will sell out.

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To register and for complete information please see our website: PAGS-cme.org.

Highlights Include

- *Optional* **Opioid REMS Course** *Free to PAGS Attendees*
- *Optional* **Hands-on Workshops**
  Limited space available. First come. First served!
  - Tissue Extraction Techniques Workshop
  - Laparoscopic Suturing
  - Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
  - Office-Based Gynecologic Procedures
- **Incontinence and Prolapse Surgery**
- **Gynecologic Oncology for the Generalist**
- **Hysterectomy Techniques**
- **Avoiding and Managing Complications**
- **Fibroid Management & Principles of Electrosurgery**
- **Surgical Tips for Successful Pelvic Surgery**

SPECIAL KEYNOTES:

- **Management of Chronic Pelvic Pain**
- **Non-Opioid Pain Management after Minimally Invasive Hysterectomy**
- *Optional* **Practice Management Program**

How to Register for PAGS

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■ **Best Buy!** PAGS + P.E.P. Discount Combination Package	$1,195	$1,395
■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future** All Day Workshop **NEW!**	$495	$595
■ **Laparoscopic Suturing** Morning Workshop	$275	$345
■ **Tissue Extraction Techniques** Morning Workshop	$275	$345
■ **Vaginal Hysterectomy & Cystourethroscopy** Afternoon Workshop	$325	$395
■ **Opioid REMS Course** *Pre-registration required*	Free	Free

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 6, 2018. After November 6, 2018 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

CONTINUED FROM PAGE 16

ARE WE USING THE RIGHT METRICS TO MEASURE CESAREAN RATES?

MYRON R. KANOFSKY, MD
(WEB EXCLUSIVE COMMENTARY; JUNE 19, 2018)

High cesarean delivery rate is related to many factors

I have been questioning the metrics, too. My cesarean delivery (CD) rate is high. Why? In my pre-retirement I do a lot of indigent work. Three public health clinics with nurse practitioners send me their patients to do their CDs. Morbid obesity is endemic among the Pacific Islanders.

Friedrich C. Bieling, MD
Tamuning, Guam

Use metrics for populations, not individuals

Dr. Kanofsky's commentary on CD metrics is 100% correct. As an ethical question for physicians and society alike, I would ask, is applying metrics to physicians even moral?

As an ObGyn for most of 4 decades, my approach to obstetrics has not changed. In some years, my CD rate was very low, and in others my rate was average. Women must be treated as individuals. Although the industrial revolution increased quality and decreased costs in manufacturing, I do not believe that we can or should apply those principles to our patients.

Government regulators, insurance companies, and many physician leaders have lost sight of the Oath of Maimonides, which states, "May the love of my art actuate me at all times; may neither avarice nor miserliness…engage my mind,"[1] as well as Hippocrates' ancient observation, "Whatsoever house I may enter, my visit shall be for the convenience and advantage of the patient."[2] In addition, in the modern version of the Hippocratic Oath that most schools use today, physicians swear to "apply, for the benefit of the sick, all measures [that] are required…"[3]—not to the benefit of the government, the federal budget, or an accountable care organization (ACO).

Clearly, the informed consent of a 42-year-old who had in vitro fertilization and has a floating presentation with a low Bishop score and an estimated fetal weight of 4,000 at 40 6/7 weeks must include not only the risks of primary CD but also the risks of a long labor that may result in a CD, the occasional risk of shoulder dystocia, or third- or fourth-degree extension. Not having had a case of shoulder dystocia or a third- or fourth-degree in more than a decade clearly justifies my rationale.

The morbidity of a multiple repeat CD or even a primary CD in an obese woman is significantly more risky than a non-labored elective CD in a woman of normal weight who plans to have only 1 or 2 children. We must individualize our care. Metrics are for populations, not individuals.

Health economists who aggressively advocate lower cesarean rates accept stillbirths and babies with hypoxic ischemic encephalopathy, cerebral palsy, or Erb's palsy as long as governmental expenditures are lowered. Do the parents of these children get a vote? The majority of practicing physicians like myself feel more aligned with the Hippocratic Oath and the Oath of Maimonides. We believe that we have a moral, ethical, and medical responsibility to the individual patient and not to an ACO or government bean counter.

I would suggest an overarching theme: choice—the freedom to make our own intelligent decisions based on reasonable data and interpretation of the medical literature.

One size does not fit all. So why do those pushing comparative metrics tell us there is only one way to practice obstetrics?

Howard C. Mandel, MD
Los Angeles, California

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1. Tan SY, Yeow ME. Moses Maimonides (1135–1204): rabbi, philosopher, physician. Singapore Med J. 2002;43(11):551–553.
2. Copland J, ed. The Hippocratic Oath. In: The London Medical Repository, Monthly Journal, and Review, Volume III. 1825;23:258.
3. Tyson P. The Hippocratic Oath today. Nova. March 27, 2001. http://www.pbs.org/wgbh/nova/body/hippocratic-oath-today.html. Accessed September 21, 2018.

HOW DOES ORAL CONTRACEPTIVE USE AFFECT ONE'S RISK OF OVARIAN, ENDOMETRIAL, BREAST, AND COLORECTAL CANCERS?

DANA M. SCOTT, MD;
MARK D. PEARLMAN, MD
(EXAMINING THE EVIDENCE; MAY 2018)

Agrees that OC use clearly reduces mortality

Recent evidence from long-term observations of hundreds of thousands of women, in 10 European countries, clearly demonstrated that the use of oral contraceptives (OCs) reduced mortality by roughly 10%.[1,2] Newer OCs increase women's overall survival.

In comparison, reducing obesity by 5 body mass index points would reduce mortality by only 5%, from 1.05 to 1.[3]

Dr. Stavros Saripanidis
Thessaloniki, Greece

References

1. Merritt MA, Riboli E, Murphy N, et al. Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition: a cohort study. BMC Med. 2015;13:252.
2. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216(6):580.e1–580.e9.
3. Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ. 2016;353:i2156.

CONTINUED ON PAGE 18

COMMENT & CONTROVERSY

CONTINUED FROM PAGE 17

HOW TO DECIDE ON PURCHASING NEW MEDICAL EQUIPMENT
DAVID S. KIM, MD, PHD, MBA
(MAY 2018)

Astonished by physician hourly rate calculation

I always enjoy the articles and incredible insights presented in OBG MANAGEMENT. Some very sophisticated, well-founded ideas are presented in the article on deciding on purchasing medical equipment. Then, however, you get to the calculations: $50 for 30 minutes of physician time!

My plumber charges me $100 for the first half hour of a visit (okay, there are lots of cliched jokes about this), but on average a physician assistant costs almost that much. It is a sad day in the business of medicine when experts value the time of highly educated physicians at $100 per hour. Maybe someday we can expect to be reasonably compensated for our efforts and training. When I advise my colleagues, I calculate their time, depending on their practice model, between $300 and $400 per hour.

Hamid Banooni, MD
Farmington Hills, Michigan

Dr. Kim responds

I thank Dr. Banooni for his comment. I agree that physicians are highly skilled and educated and that their time deserves to be valued at more than $100 per hour. In the article and the example provided, the values (revenues, costs, and so on) were not meant to be exactly representative of the marketplace, but instead were used merely as an example for understanding the calculation tools for purchasing medical equipment. That being said, I arrived at the $100 per hour cost for physician time (included in the variable cost in the Figure, "Breakeven analysis for hysteroscope purchase for use in tubal sterilization") for 2 primary reasons. First, to simplify the calculation, and second, to use an equivalent universal hourly salary ($100 per hour) for a physician's comparative labor cost in the marketplace. Currently, the median hourly compensation for an ObGyn laborist is $110 per hour.[1] To simplify, I rounded down to $100. I wholeheartedly agree with Dr. Banooni, however, that a physician's time should be valued higher in society.

Reference

1. Society of Ob/Gyn Hospitalists. SOGH 2016 hospitalist employment and salary survey. 2016. https://www.societyofobgynhospitalists.org/assets/SOGH%202016%20Salary%20%20Employment%20Survey.pdf. Accessed September 24, 2018.

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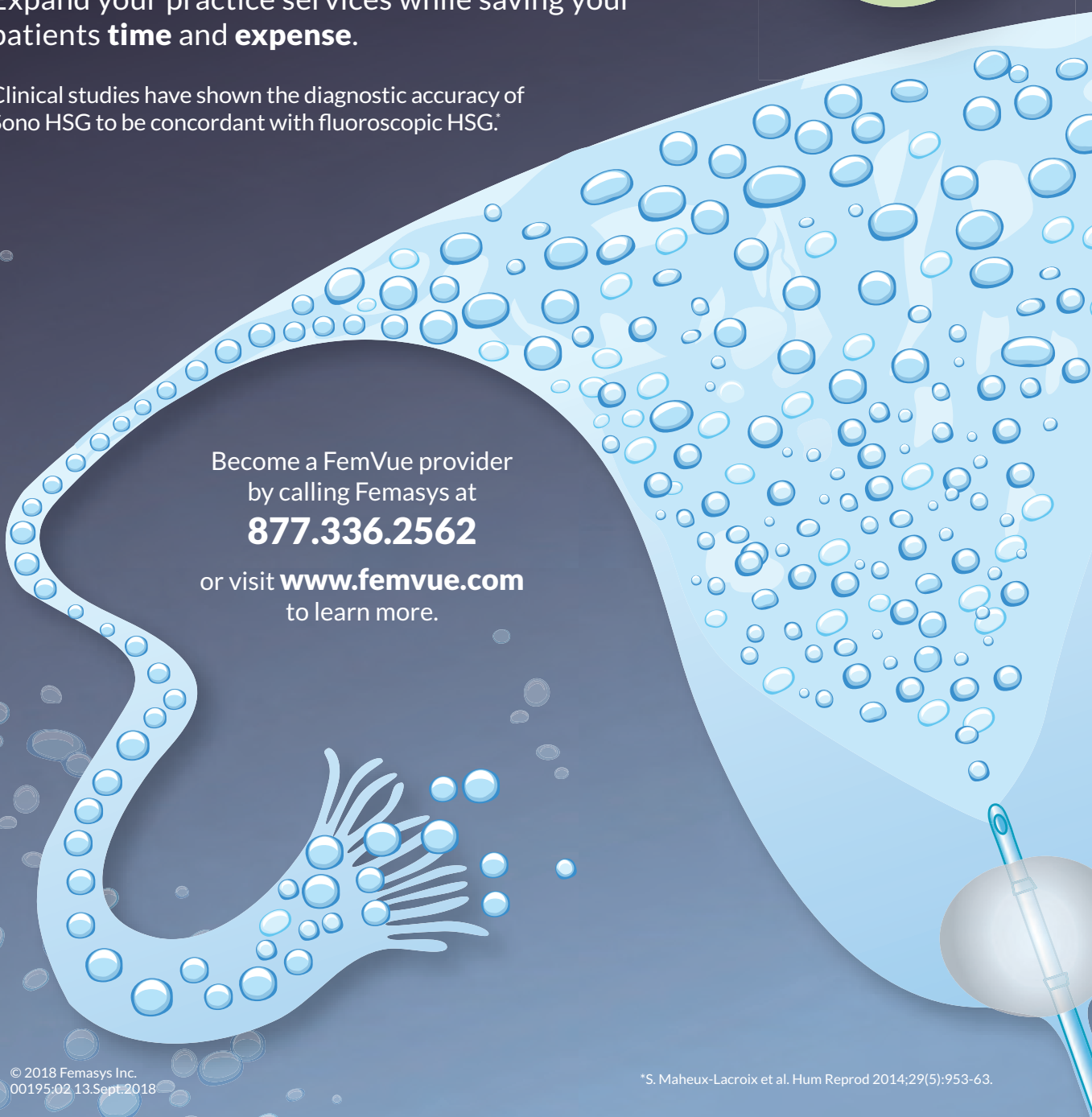

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*S. Maheux-Lacroix et al. Hum Reprod 2014;29(5):953-63.

Myomectomy of a large cervical fibroid in a patient desiring future fertility

A technique for myomectomy with uterine preservation in a 33-year-old woman with a 20-cm cervical fibroid, as well as a strategy for preoperative planning (meant to reduce this surgery's high risk for blood loss, urologic injury, and hysterectomy)

Morgan Booher, DO; Mitchell Edelson, MD; David Jaspan, DO; and Jay Goldberg, MD, MSCP

IN THIS ARTICLE

Uterine fibroids are the most common tumors of the uterus. Clinically significant fibroids that arise from the cervix are less common.[1] Removing large cervical fibroids when a patient desires future fertility is a surgical challenge because of the risks of significant blood loss, bladder and ureteral injury, and unplanned hysterectomy. For women who desire future fertility, myomectomy can improve the chances of pregnancy by restoring normal anatomy.[2] In this article, we describe a technique for myomectomy with uterine preservation in a patient with a 20-cm cervical fibroid.

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Dr. Goldberg reports that he is on the advisory board and speakers bureau for AbbVie. The other authors report no financial relationships relevant to this article.

CASE Woman with increasing girth and urinary symptoms is unable to conceive

A 33-year-old white woman with a history of 1 prior vaginal delivery presents with symptoms of increasing abdominal girth, intermittent urinary retention and urgency, and inability to become pregnant. She reports normal monthly menstrual periods. On pelvic examination, the ObGyn notes a large fibroid partially protruding through a dilated cervix. Abdominal examination reveals a fundal height at the level of the umbilicus.

Transvaginal ultrasonography shows a uterus that measures 4.5 x 6.1 x 13.6 cm. Arising from the posterior aspect of the uterine fundus, body, and lower uterine segment is a fibroid that measures 9.7 x 15.5 x 18.9 cm. Magnetic resonance imaging is performed and confirms a fibroid measuring 10 x 16 x 20 cm. The inferiormost aspect of the fibroid appears to be within the endometrial cavity and cervical canal. Most of the fibroid, however, is posterior to the uterus, pressing on and anteriorly displacing the endometrial cavity (**FIGURE 1**).

What is your surgical approach?

Comprehensive preoperative planning

In this case, the patient should receive extensive preoperative counseling about the significantly increased risk for hysterectomy with an attempted myomectomy. Prior to being scheduled for surgery, she also should have a consultation with a gynecologic oncologist. To optimize visualization during the procedure, we recommend to plan for a midline vertical skin incision. Because of the potential bleeding risks, blood products should be made available in the operating room at the time of surgery.

Techniques for surgery

Intraoperatively, a vertical midline incision exteriorizes the uterus from the peritoneal cavity. Opening of the retroperitoneal spaces allows for identification of the ureters. Perform dissection in the midline away from the ureters. Inject vasopressin (5 U) into the uterine fundus. Incise the uterine serosa over the myoma posteriorly in the midline.

Perform a myomectomy, with gentle "shelling out" of the myoma; in this way the specimen can be removed intact. Reapproximate the fibroid cavity in 3 layers with 0-Vicryl (polyglactin 910) suture in a running fashion (**FIGURE 2,** page 22).

CASE Resolved

The estimated blood loss during surgery was 50 mL. Final pathology reported a 1,660-g intact myoma. The patient's postoperative course was uncomplicated and she was discharged home on postoperative day 1.

Her postoperative evaluation was 1 month later. Her abdominal incision was well healed. Her fibroid-related symptoms had resolved, and she planned to attempt pregnancy. Cesarean delivery for future pregnancies was recommended.

Increase the chances of a good outcome

Advanced planning for attempted myomectomy of a large cervical fibroid can increase the probability of a successful outcome. We suggest the following:

Counsel the patient on risks. Our preoperative strategy includes extensive counseling on the significantly increased surgical risks and the possibility of unavoidable hysterectomy. Given the anatomic distortion with respect to the ureters, bladder, and major blood vessels, involving gynecologic oncology is beneficial to the surgery planning process.

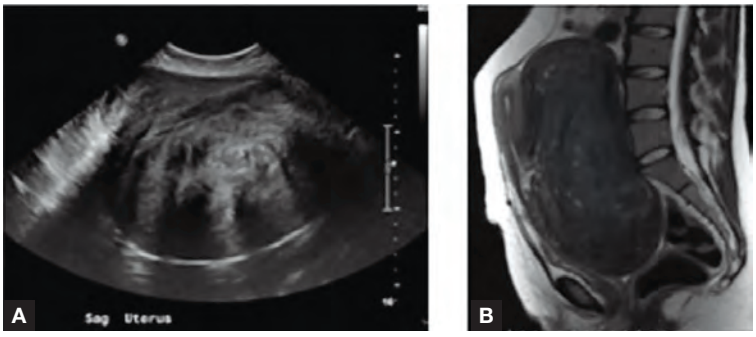
Prepare for possible transfusion. Ensure blood products are made available in the operating room in case transfusion is needed.

Control bleeding. Randomized studies have shown that intrauterine injection of vasopressin, through its action as a vasoconstrictor, decreases surgical bleeding.[3,4] While little data are available on vasopressin's most effective dosage and dilution, 5 U at a very dilute concentration (0.1–0.2 U/mL) has been recommended.[5] A midline cervical incision away from lateral structures and gentle shelling out of the cervical fibroid help to avoid intraoperative damage to the bladder, ureters, and vascular supply.

Close in multiple layers. This approach can prevent a potential space for hematoma accumulation.[6] Further, a multiple-layer closure of a myometrial incision may decrease the risk for uterine rupture in subsequent pregnancies.[7]

Advise abstinence postsurgery. There are no consistent data to guide patient counseling regarding recommendations for the timing of

FIGURE 1 Imaging pinpoints the location of a large uterine fibroid

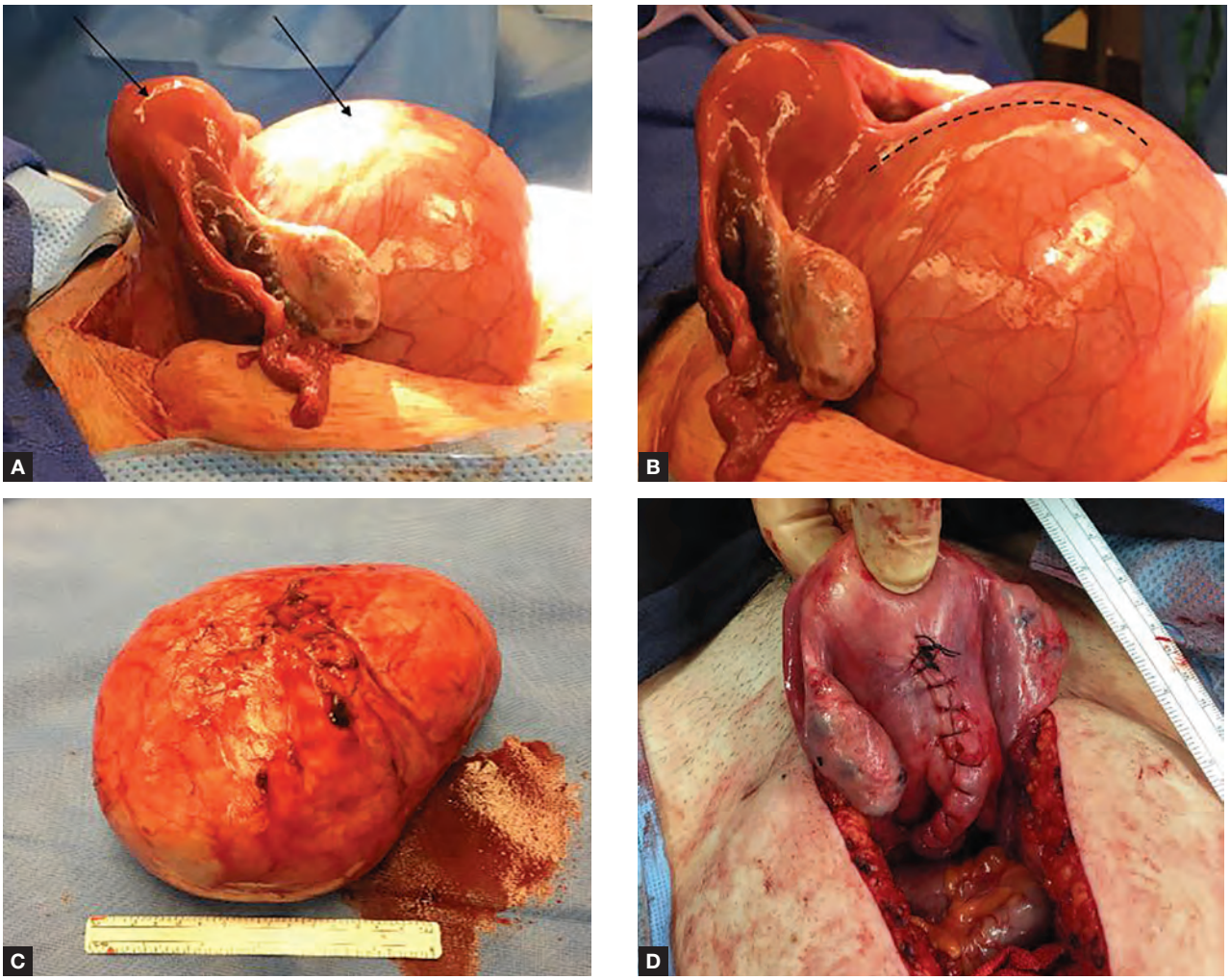


Transabdominal ultrasonography scan (**A**) and MRI scan (**B**) show a 20-cm fibroid that arises from the posterior uterus and extends inferiorly into the lower uterine segment and cervix.
Abbreviation: MRI, magnetic resonance imaging.

FAST TRACK

Preoperative strategy includes extensive counseling on the significantly increased surgical risks of myomectomy for a large fibroid and the possibility of unavoidable hysterectomy

FIGURE 2 Our procedures for removing a 20-cm cervical fibroid



(**A**) Vasopressin injection into the uterus and posterior aspect (arrows) of the fibroid. (**B**) A 10-cm incision (dotted line) made through the posterior lower uterine segment and fibroid serosa. (**C**) Intact removal of the capsule after "shelling out" the fibroid. (**D**) Closure of the fibroid capsule overlying the lower uterine segment and cervix, using 3 layers with 0-Vicryl (polyglactin 910) suture in a running, locking fashion.

conception following myomectomy. We counseled our patient to abstain from vaginal intercourse for 4 weeks, after which time she soon should attempt to conceive. Although there are no published data regarding when it is best to resume sexual relations following such a surgery, we advise a 1-month period primarily to allow healing of the skin incision. Any further delay in attempting to become pregnant may allow for the growth of additional fibroids.

Plan for future deliveries. When the myoma is extensively involved, such as in this case, we recommend cesarean delivery for future pregnancies to avoid the known risk of uterine rupture.[8] In general, we recommend cesarean delivery in future pregnancies if an incision larger than 50% of the myometrial thickness is made in the contractile portion of the uterus.

Final takeaway. Despite increased surgical risks, myomectomy of a large cervical fibroid is possible and can alleviate symptoms and improve future fertility. ●

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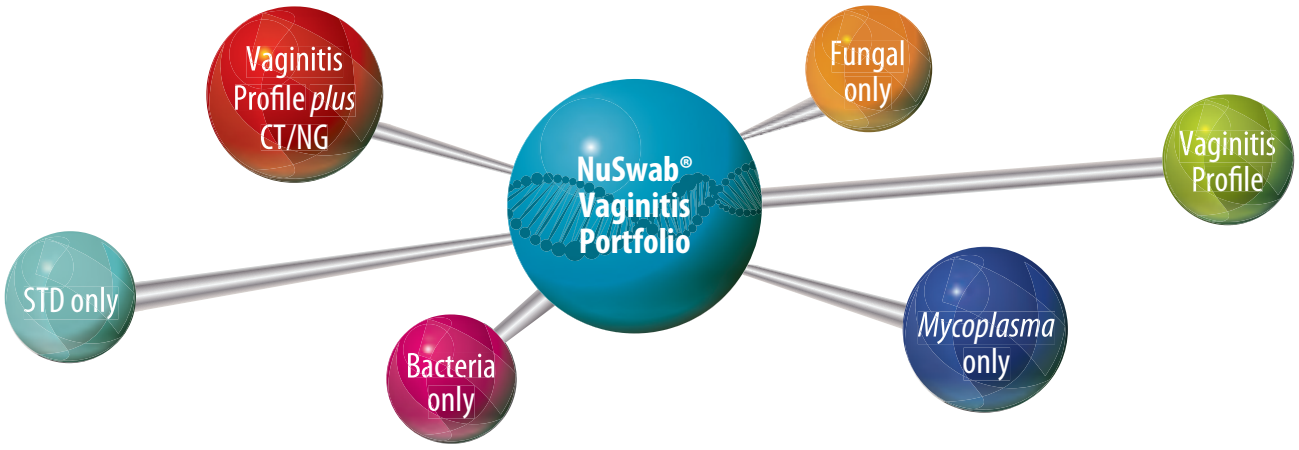

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"To cysto or not to cysto?" that is the ongoing question surrounding the role of cystoscopy following benign gyn surgery. These authors review data on the procedure's ability to detect injury, an ideal method for visualizing ureteral efflux, and how universal cystoscopy can affect the rate of injury.

Using cystoscopy to evaluate ureteral efflux and bladder integrity following benign gynecologic surgery increases the detection rate of urinary tract injuries.[1] Currently, it is standard of care to perform a cystoscopy following anti-incontinence procedures, but there is no consensus among ObGyns regarding the use of universal cystoscopy following benign gynecologic surgery.[2] A number of studies, however, have suggested potential best practices for evaluating urinary tract injury during pelvic surgery for benign gynecologic conditions.

Pelvic surgeries for benign gynecologic conditions, including fibroids, menorrhagia, and pelvic organ prolapse (POP), are common. More than 500,000 hysterectomies are performed annually in the United States, and up to 11% of women will undergo at least one surgery for POP or urinary incontinence in their lifetime.[3,4] During gynecologic surgery, the urinary tract is at risk, and the injury rate ranges from 0.02% to 2% for ureteral injury and from 1% to 5% for bladder injury.[5,6]

In a recent large randomized controlled trial, the rate of intraoperative ureteral obstruction following uterosacral ligament suspension (USLS) was 3.2%.[7] Vaginal vault suspensions, as well as other vaginal cuff closure techniques, are common procedures associated with urinary tract injury.[8] Additionally, ureteral injury during surgery for POP occurs in as many as 2% of anterior vaginal wall repairs.[9]

It is well documented that a delay in diagnosis of ureteral and/or bladder injuries is associated with increased morbidity, including the need for additional surgery to repair the injury; in addition, significant delay in identifying an injury may lead to subsequent sequela, such as renal injury and fistula formation.[8]

A large study in California found that 36.5% of hysterectomies performed for POP

IN THIS ARTICLE

were performed by general gynecologists.[10] General ObGyns performing these surgeries therefore must understand the risk of urinary tract injury during hysterectomy and reconstructive pelvic procedures so that they can appropriately identify, evaluate, and repair injuries in a timely fashion.

The best way to identify urinary tract injury at the time of gynecologic surgery is by cystoscopy, including a bladder survey and ureteral efflux evaluation. When should a cystoscopy be performed, and what is the best method for visualizing ureteral efflux? Can instituting universal cystoscopy for all gynecologic procedures make a difference in the rate of injury detection? In this Update, we summarize the data from 4 studies that help to answer these questions.

About 30% of urinary tract injuries identified prior to cystoscopy at hysterectomy (which detected 5 of 6 injuries)

FAST TRACK

At hysterectomy, the total urinary tract injury rate detected by cystoscopy was 4.8%, with the ureteral injury rate 1.7% and the bladder injury rate 3.6%

Vakili B, Chesson RR, Kyle BL, et al. The incidence of urinary tract injury during hysterectomy: a prospective analysis based on universal cystoscopy. Am J Obstet Gynecol. 2005;192(5):1599–1604.

Vakili and colleagues conducted a multicenter prospective cohort study of women undergoing hysterectomy for benign indications; cystoscopy was performed in all cases. The 3 hospitals involved were all part of the Louisiana State University Health system. The investigators' goal was to determine the rate of urinary tract injury in this patient population at the time of intraoperative cystoscopy.

Intraoperative cystoscopy beats visual evaluation

Four hundred and seventy-one women underwent hysterectomy and had intraoperative cystoscopy, including evaluation of ureteral patency with administration of intravenous (IV) indigo carmine. Patients underwent abdominal, vaginal, or laparoscopic hysterectomy, and 54 (11.4%) had concurrent POP or anti-incontinence procedures. The majority underwent an abdominal hysterectomy (59%), 31% had a vaginal hysterectomy, and 10% had a laparoscopic-assisted vaginal hysterectomy or total laparoscopic hysterectomy.

Rate of urinary tract injuries. The total urinary tract injury rate detected by cystoscopy was 4.8%. The ureteral injury rate was 1.7%, and the bladder injury rate was 3.6%. A combined ureteral and bladder injury occurred in 2 women.

Surgery for POP significantly increased the risk of ureteral injury (7.3% vs 1.2%; $P = .025$). All cases of ureteral injury during POP surgery occurred during USLS. There was a trend toward a higher rate of bladder injury in the group with concurrent anti-incontinence surgery (12.5% vs 3.1%; $P = .049$). Regarding the route of hysterectomy, the vaginal approach had the highest rate of ureteral injury; however, when prolapse cases were removed from the analysis, there were no differences between the abdominal, vaginal, and laparoscopic approaches for ureteral or bladder injuries.

Injury detection with cystoscopy. Importantly, the authors found that only 30% of injuries were identified prior to performing intraoperative cystoscopy. The majority

CONTINUED ON PAGE 28

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of these were bladder injuries. In addition, despite visual confirmation of ureteral peristalsis during abdominal hysterectomy, when intraoperative cystoscopy was performed with evaluation for ureteral efflux, 5 of 6 ureteral injury cases were identified. The authors reported 1 postoperative vesicovaginal fistula and concluded that it was likely due to an unrecognized bladder injury. No other undetected injuries were identified.

Notably, no complications occurred as a result of cystoscopy.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The rate of urinary tract injury, including both bladder and ureteral injuries, was more than 4% at the time of hysterectomy for benign conditions. Using intraoperative peristalsis or normal ureteral caliber could result in a false sense of security since these are not reliable signs of ureteral integrity. The majority of urinary tract injuries will not be identified without cystoscopic evaluation.

Multiple surgical indications reflect real-world scenario

The study included physicians from 3 different hospitals and all routes of hysterectomy for multiple benign gynecologic indications as well as concomitant pelvic reconstructive procedures. While this enhances the generalizability of the study results, all study sites were located in Louisiana at hospitals with resident trainee involvement. Additionally, this study confirms previous retrospective studies that reported higher rates of injury with pelvic reconstructive procedures.

The study is limited by the inability to blind surgeons, which may have resulted in the surgeons altering their techniques and/or having a heightened awareness of the urinary tract. However, their rates of ureteral and bladder injuries were slightly higher than previously reported rates, suggesting that the procedures inherently carry risk. The study is further limited by the lack of a retrospective comparison group of hysterectomy without routine cystoscopy and a longer follow-up period that may have revealed additional missed delayed urologic injuries.

FAST TRACK

The majority of urinary tract injuries during hysterectomy will not be identified without cystoscopic evaluation

Universal cystoscopy policy proves protective, surgeon adherence is high

Chi AM, Curran DS, Morgan DM, Fenner DE, Swenson CW. Universal cystoscopy after benign hysterectomy: examining the effects of an institutional policy. Obstet Gynecol. 2016;127(2):369–375.

In a retrospective cohort study, Chi and colleagues evaluated urinary tract injuries at the time of hysterectomy before and after the institution of a universal cystoscopy policy. At the time of policy implementation at the University of Michigan, all faculty who performed hysterectomies attended a cystoscopy workshop. Attending physicians without prior cystoscopy training also were proctored in the operating room for 3 sessions and were required to demonstrate competency with bladder survey, visualizing ureteral efflux, and urethral assessment. Indigo carmine was used to visualize ureteral efflux.

Detection of urologic injury almost doubled with cystoscopy

A total of 2,822 hysterectomies were included in the study, with 973 in the pre–universal cystoscopy group and 1,849 in the post–universal cystoscopy group. The study period was 7 years, and data on complications were abstracted for 1 year

after the completion of the study period.

The primary outcome had 3 components:

- the rate of urologic injury before and after the policy
- the cystoscopy detection rate of urologic injury
- the adherence rate to the policy.

The overall rate of bladder and ureteral injury was 2.1%; the rate of injury during pre–universal screening was 2.6%, and during post–universal screening was 1.8%. The intraoperative detection rate of injury nearly doubled, from 24% to 47%, when intraoperative cystoscopy was utilized. In addition, the percentage of delayed urologic complications decreased from 28% to 5.9% (P = .03) following implementation of the universal cystoscopy policy. With regard to surgeon adherence, cystoscopy was documented in 86.1% of the hysterectomy cases after the policy was implemented compared with 35.7% of cases before the policy.

The investigators performed a cost analysis and found that hospital costs were nearly twice as much if a delayed urologic injury was diagnosed.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Instituting a universal cystoscopy policy for hysterectomy was associated with a significant decrease in delayed postoperative urinary tract complications and an increase in the intraoperative detection rate of urologic injuries. Intraoperative detection and repair of a urinary tract injury is cost-effective compared with a delayed diagnosis.

Study had many strengths

This study evaluated aspects of implementing quality initiatives after proper training and proctoring of a procedure. The authors compared very large cohorts from a busy academic medical center in which surgeon adherence with routine cystoscopy was high. The majority of patient outcomes were tracked for an extended period following surgery, thereby minimizing the risk of missing delayed urologic injuries. Notably, however, there was shorter follow-up time for the post–universal cystoscopy group, which could result in underestimating the rate of delayed urologic injuries in this cohort.

FAST TRACK

The percentage of delayed urologic complications decreased from 28% to 5.9% (P = .03) following implementation of a universal cystoscopy policy

Cystoscopy reveals ureteral obstruction during various vaginal POP repair procedures

Gustilo-Ashby AM, Jelovsek JE, Barber MD, Yoo EH, Paraiso MF, Walters MD. The incidence of ureteral obstruction and the value of intraoperative cystoscopy during vaginal surgery for pelvic organ prolapse. Am J Obstet Gynecol. 2006;194(5):1478–1485.

To determine the rate of ureteral obstruction and ureteral injury during vaginal surgery for POP and the accuracy of using intraoperative cystoscopy to prevent upper urinary tract morbidity, Gustilo-Ashby and colleagues performed a retrospective review study of a large patient cohort.

Cystoscopy with indigo carmine is highly sensitive

The study included 700 patients who underwent vaginal surgery for anterior and/or apical POP. Patients had 1 or more of the following anterior and apical prolapse repair procedures: USLS (51%), distal McCall culdeplasty (26%), proximal McCall culdeplasty (29%), anterior colporrhaphy (82%), and colpocleisis (1.4%). Of note, distal McCall culdeplasty was defined as incorporation of the "vaginal epithelium into the uterosacral plication," while proximal McCall culdeplasty involved plication of "the uterosacral

ligaments in the midline proximal to the vaginal cuff." All patients were given IV indigo carmine to aid in visualizing ureteral efflux.

The majority of patients had a hysterectomy (56%). When accounting for rare false-positive and negative cystoscopy results, the overall ureteral obstruction rate was 5.1% and the ureteral injury rate was 0.9%. The majority of obstructions occurred with USLS (5.9%), proximal McCall culdeplasty (4.4%), and colpocleisis (4.2%). Ureteral injuries occurred only in 6 cases: 3 USLS and 3 proximal McCall culdeplasty procedures.

Based on these findings, the authors calculated that cystoscopy at the time of vaginal surgery for anterior and/or apical prolapse has a sensitivity of 94.4% and a specificity of 99.5% for detecting ureteral obstruction. The positive predictive value of cystoscopy with the use of indigo carmine for detection of ureteral obstruction is 91.9% and the negative predictive value is 99.7%.

Impact of indigo carmine's unavailability

This study's strengths include its large sample size and the variety of surgical approaches used for repair of anterior vaginal wall and apical prolapse. Its retrospective design, however, is a limitation; this could result in underreporting of ureteral injuries if patients received care at another institution after surgery. Furthermore, it is unclear if cystoscopy would be as predictive of ureteral injury without the use of indigo carmine, which is no longer available at most institutions.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The utility of cystoscopy with IV indigo carmine as a screening test for ureteral obstruction is highlighted by the fact that most obstructions were relieved by intraoperative suture removal following positive cystoscopy. McCall culdeplasty procedures are commonly performed by general ObGyns at the time of vaginal hysterectomy. It is therefore important to note that rates of ureteral obstruction after proximal McCall culdeplasty were only slightly lower than those after USLS.

FAST TRACK

For detecting ureteral obstruction, the authors calculated that cystoscopy at the time of vaginal surgery for anterior and/or apical prolapse has a sensitivity of 94.4% and specificity of 99.5%

Sodium fluorescein and 10% dextrose provide clear visibility of ureteral jets in cystoscopy

Espaillat-Rijo L, Siff L, Alas AN, et al. Intraoperative cystoscopic evaluation of ureteral patency: a randomized controlled trial. Obstet Gynecol. 2016;128(6):1378–1383.

In a multicenter randomized controlled trial, Espaillat-Rijo and colleagues compared various methods for visualizing ureteral efflux in participants who underwent gynecologic or urogynecologic procedures in which cystoscopy was performed.

Study compared 4 media

The investigators enrolled 176 participants (174 completed the trial) and randomly assigned them to receive 1 of 4 modalities: 1) normal saline as a bladder distention medium (control), 2) 10% dextrose as a bladder distention medium, 3) 200 mg oral phenazopyridine given 30 minutes prior to cystoscopy, or 4) 50 mg IV sodium fluorescein at the start of cystoscopy. Indigo carmine was not included in this study because

CONTINUED ON PAGE 32

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it has not been routinely available since 2014.

Surgeons were asked to categorize the ureteral jets as "clearly visible," "somewhat visible," or "not visible."

The primary outcome was subjective visibility of the ureteral jet with each modality during cystoscopy. Secondary outcomes included surgeon satisfaction, adverse reactions to the modality used, postoperative urinary tract infection, postoperative urinary retention, and delayed diagnosis of ureteral injury.

Visibility assessment results. Overall, ureteral jets were "clearly visible" in 125 cases (71%) compared with "somewhat visible" in 45 (25.6%) and "not visible" in 4 (2.3%) cases. There was a statistically significant difference between the 4 groups. Use of sodium fluorescein and 10% dextrose resulted in significantly better visualization of ureteral jets ($P<.001$ and $P = .004$, respectively) compared with the control group. Visibility with phenazopyridine was not significantly different from that in the control group or in the 10% dextrose group (**FIGURE**).

Surgeon satisfaction was highest with 10% dextrose and sodium fluorescein. In 6 cases, the surgeon was not satisfied with visualization of the ureteral jets and relied on fluorescein (5 times) or 10% dextrose (1 time) to ultimately see efflux. No significant adverse events occurred; the rate of urinary tract infection was 24.1% and did not differ between groups.

Results are widely generalizable

This was a well-designed randomized multicenter trial that included both benign gynecologic and urogynecologic procedures, thus strengthening the generalizability of the study. The study was timely since proven methods for visualization of ureteral patency became limited with the withdrawal of commercially available indigo carmine, the previous gold standard. ●

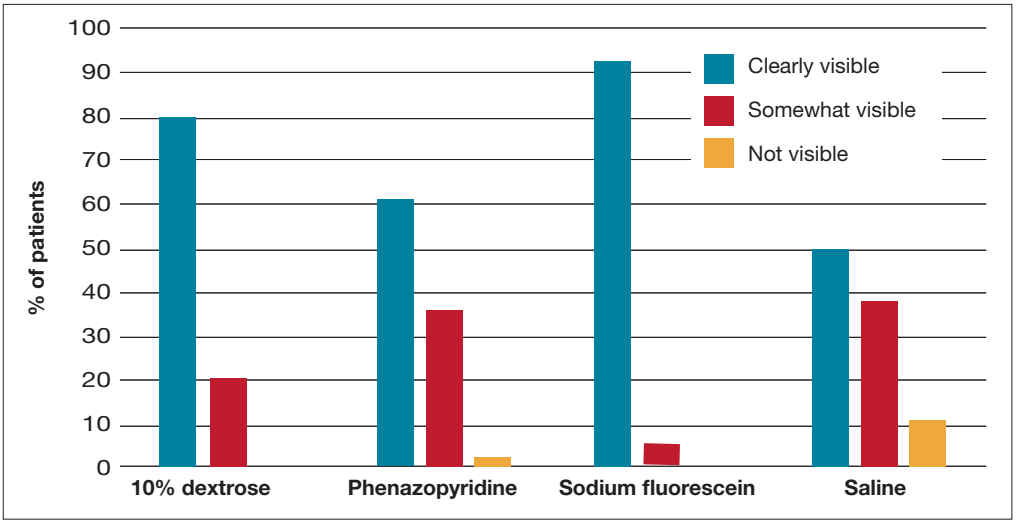
WHAT THIS EVIDENCE MEANS FOR PRACTICE

Intravenous sodium fluorescein and 10% dextrose as bladder distention media can both safely be used to visualize ureteral efflux and result in high surgeon satisfaction. Although 10% dextrose has been associated with higher rates of postoperative urinary tract infection,[11] this was not found to be the case in this study. Preoperative administration of oral phenazopyridine was no different from the control modality with regard to visibility and surgeon satisfaction.

FAST TRACK

Use of sodium fluorescein and 10% dextrose in cystoscopy resulted in significantly better visualization of ureteral jets compared with the control group

FIGURE Ratings of modalities used in cystoscopy for visualization of ureteral jets[12]



The cost-effectiveness consideration

The debate around universal cystoscopy following benign gynecologic surgery is ongoing. The studies discussed in this Update demonstrate that cystoscopy following hysterectomy for benign indications:

- is superior to visualizing ureteral peristalsis
- increases detection of urinary tract injuries, and
- decreases delayed urologic injuries.

Although these articles emphasize the importance of detecting urologic injury, the picture would not be complete without mention of cost-effectiveness. Only one study, from 2001, has evaluated the cost-effectiveness of universal cystoscopy.[1] Those authors concluded that universal cystoscopy is cost-effective only when the rate of urologic injury is 1.5% to 2%, but this conclusion, admittedly, was limited by the lack of data on medicolegal settlements, outpatient expenses, and nonmedical-related economic loss from decreased productivity. Given the extensive changes that have occurred in medical practice over the last 17 years and the emphasis on quality metrics and safety, an updated analysis would be needed to make definitive conclusions about cost-effectiveness.

While this Update cannot settle the ongoing debate of universal cystoscopy in gynecology, it is important to remember that the American College of Obstetricians and Gynecologists and the American Urogynecologic Society recommend cystoscopy following all surgeries for pelvic organ prolapse and stress urinary incontinence.[2]

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WATCH FOR...

›› Update on minimally invasive gynecologic surgery

Arnold P. Advincula, MD

AVOIDING OBSTETRIC EMERGENCIES

Diagnosing placenta accreta spectrum with prenatal ultrasound

Up to half of all placenta accreta spectrum cases escape prenatal detection. Consensus is that ultrasonography (US) should be the primary imaging modality. In this expert guide on identification, the authors describe the use of diagnostic US markers at their institution and address standardization, sensitivity, and specificity.

Jennifer Philips, MD, and Alfred Abuhamad, MD

IN THIS ARTICLE

ON THE WEB

What is the diagnostic accuracy of US for PAS?
at mdedge.com/obgyn

Placenta accreta spectrum (PAS) describes abnormal invasion of placental tissue into or through the myometrium, comprising 3 distinct conditions: *placenta accreta*, *placenta increta*, and *placenta percreta*. This complication is relatively new to obstetrics, first described in 1937.[1]

The overall incidence of PAS has been increasing over several decades, in parallel to an increasing rate of cesarean delivery (CD), with an incidence from 1982 through 2002 of 1 in 533 pregnancies, representing a 5-fold increase since the 1980s.[2] PAS is associated with significant morbidity and mortality, including fetal growth restriction, preterm delivery, placental abruption antenatally, and hemorrhage during delivery or postpartum.

Prenatal diagnosis of PAS and planned delivery at an experienced center are associated with significant reduction in maternal and fetal morbidity.[3] In an era of advanced imaging modalities, prenatal detection of PAS regrettably remains variable and largely subjective: As many as 20% to 50% of cases of PAS escape prenatal diagnosis.[3,4]

In this article, we review the sonographic markers of PAS, including diagnostic accuracy, and propose a standardized approach to prenatal diagnosis. Throughout our discussion, we describe protocols for detection of PAS practiced at our Maternal-Fetal Medicine Program in the Department of Obstetrics and Gynecology, Eastern Virginia Medical School (also see "US evaluation of PAS risk: The authors' recommended approach," page 42).

Dr. Philips is a Fellow in the Maternal-Fetal Medicine Program, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, Virginia.

Dr. Abuhamad is Mason C. Andrews Professor and Chair, Department of Obstetrics and Gynecology, and Vice Dean for Clinical Affairs, Eastern Virginia Medical School.

The authors report no financial relationships relevant to this article.

Numerous risk factors

There are many risk factors for PAS, including prior uterine surgery or instrumentation, such as CD, uterine curettage, myomectomy, pelvic radiation, and endometrial ablation. Other risk factors include smoking, in vitro fertilization, advanced maternal age, multi-

parity, and a brief interval between prior CD and subsequent pregnancy.[5] Of major significance is the increased risk of PAS in the presence of placenta previa with prior CD.[6] Knowledge of clinical risk factors by the interpreting physician appears to be associated with improved detection of PAS on ultrasonography (US).[4]

Ultrasonographic markers of PAS

First-trimester markers

Sonographic markers of PAS in the first trimester include:

- a gestational sac implanted in the lower uterine segment or in a CD scar
- multiple hypoechoic spaces within the placenta (lacunae).[7]

Lower uterine-segment implantation has been defined by Ballas and colleagues as 1) a gestational sac implanted in the lower one-third of the uterus between 8 and 10 weeks' gestation or 2) a gestational sac occupying primarily the lower uterine segment from 10 weeks' gestation onward (**FIGURE 1**, page 36).[8] Our experience is that it is difficult to accurately assess lower uterine-segment implantation beyond 13 weeks of gestation because the sac typically expands to fill the upper uterine cavity.

Color Doppler US can help differentiate lower uterine-segment implantation from a gestational sac of a failed pregnancy in the process of expulsion by demonstrating loss of circumferential blood flow in the failed pregnancy. Furthermore, applying pressure to the anterior surface of the uterus will result in downward movement of the gestational sac of a failed pregnancy.[9]

Not all gestational sacs that implant in the lower uterine segment lead to PAS: Subsequent normal pregnancies have been reported in this circumstance. In such cases, a normal thick myometrium is noted anterior to the gestational sac.[7] A patient with lower uterine-segment implantation without evidence of anterior myometrial thinning remains at risk for third-trimester placenta previa.[7]

Cesarean scar pregnancy carries significant risk of PAS. In these cases, the gestational sac is typically implanted within the scar, resulting in a thin anterior myometrium and significantly increased vascularity of the placental–myometrial and bladder–uterine wall interfaces (**FIGURE 2,** page 36).[9] Differentiating cesarean scar pregnancy from a lower uterine-segment implantation is easier to perform before the eighth week of gestation but becomes more difficult as pregnancy advances. Although it might be useful to distinguish between true cesarean scar pregnancy and lower uterine-segment implantation adjacent to or involving the scar, both carry considerable risk of PAS and excessive hemorrhage, and the approach to treating both conditions is quite similar.

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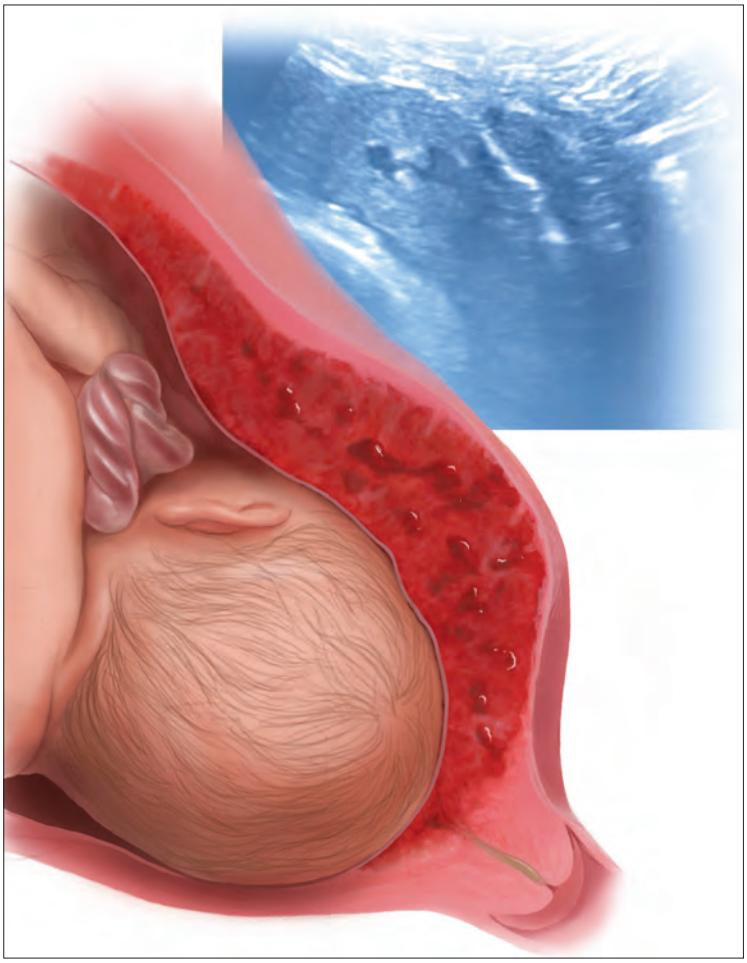
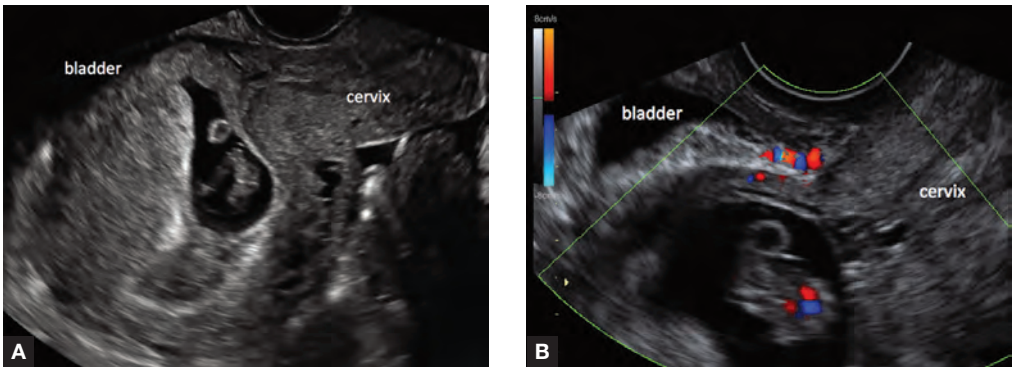


Anterior placental location, loss of "the clear space between the placenta and uterus," and the presence of multiple lacunae within the placenta are ultrasound markers of placenta accreta spectrum.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

CONTINUED FROM PAGE 35

FIGURE 1 Two fetuses: Transvaginal US, mid-sagittal plane



Scans at 8 weeks' (A) and 9 weeks' gestation (B) demonstrate gestational sac implantation in the lower one-third of the uterus. Both sacs can be seen at the level of the internal os, directly posterior to the bladder wall. Thickening of the bladder wall is evident in B, with increased flow on color Doppler evaluation.

FAST TRACK

US evaluation in the 2nd trimester should be for placental location and for the finding of multiple hyperechoic vascular spaces within the placenta parenchyma

Lacunae, with or without documented blood flow on color Doppler US, are the third marker of PAS in the first trimester.[8] Although some retrospective series and case reports describe the finding of lacunae in the first trimester of patients with diagnosed PAS, more recent literature suggests that these spaces are seen infrequently and at a similar frequency in women with and without PAS at delivery.[7]

Second- and third-trimester markers

Multiple diagnostic sonographic markers of PAS have been described in the second and third trimesters.

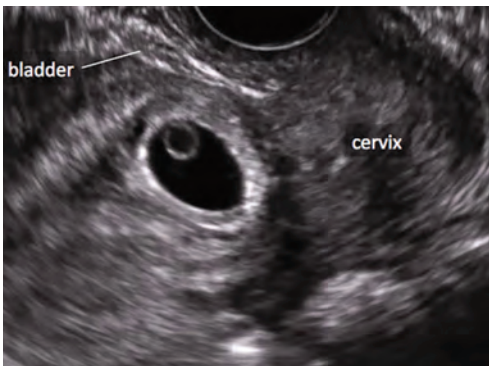
Placental location is a significant risk factor for PAS. Placenta previa in the setting of prior CD carries the highest risk of PAS—as high as 61% in women with both placenta previa and a history of 3 CDs.[10] An anterior placenta appears to be a stronger risk factor for PAS than a posterior placenta in women with prior CD; the location of the placenta should therefore be evaluated in all women in the second trimester.

Lacunae. The finding of multiple hypoechoic vascular spaces within the placental parenchyma has been associated with PAS (**FIGURES 3 AND 4,** page 38). The pathogenesis of this finding is probably related to alterations

AT OUR INSTITUTION…

…we define a first-trimester lower uterine-segment implantation as a gestational sac located just posterior to an empty bladder on transvaginal US examination. Special attention is then given to an anterior location of the placenta, and color Doppler US is applied to assess for surrounding vascularity. A cesarean scar implantation is diagnosed when the gestational sac is seen embedded into the cesarean scar, typically with a fusiform shape.

FIGURE 2 Cesarean scar pregnancy: Sonographic mid-sagittal plane



On a scan at 8 weeks' gestation, the gestational sac is anchored at the level of the cesarean section scar and has a fusiform shape. The bladder is empty but visible as a hyperechoic structure anterior to the sac.

CONTINUED ON PAGE 38

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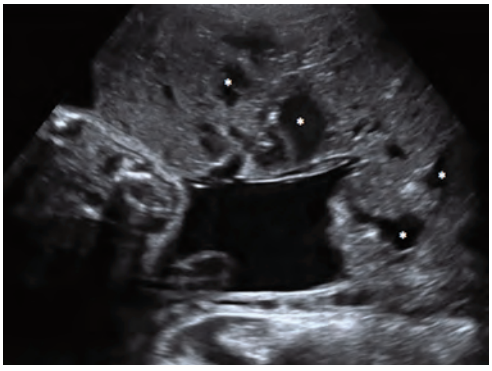
FIGURE 3 Anterior placenta accreta: Sonographic mid-sagittal plane



A scan at 32 weeks' gestation reveals multiple lacunae (asterisks).

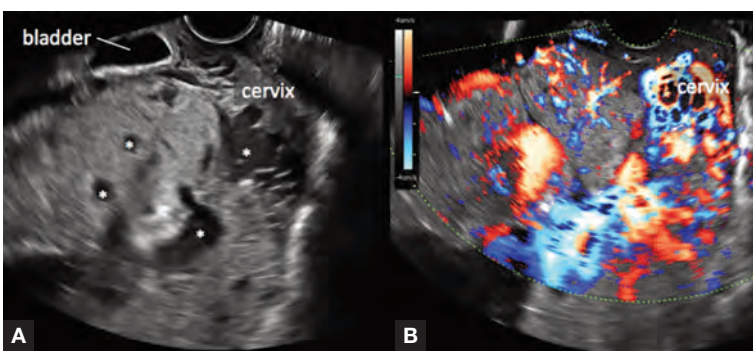
in placental tissue resulting from long-term exposure to pulsatile blood flow.[11]

Finberg and colleagues introduced a grading system for placental lacunae in 1992 that is still used:

- *Grade 0:* no lacunae seen
- *Grade 1:* 1 to 3 lacunae seen
- *Grade 2:* 4 to 6 lacunae seen
- *Grade 3:* multiple lacunae seen throughout the placenta.[12]

The sensitivity and specificity of lacunae as an independent marker for PAS have been reported to be 77% and 95%, respectively.[13] Despite these findings, several studies report a range of sensitivity (73% to 100%) and negative predictive value (88% to 100%).[14] Even in Finberg's original work, 27% of cases of confirmed PAS had Grade 0 or Grade 1 placental lacunae and 11% of cases of placenta previa, *without* PAS, demonstrated Grade 2 lacunae.[12] There is agreement, however, that, the more lacunae, the higher the risk of PAS.

FIGURE 4 Cervix and anterior placenta accreta: Sonographic mid-sagittal plane



Views in gray-scale (A) and color Doppler (B) US at 35 weeks' gestation reveal multiple lacunae in A and vascular invasion of the cervix in B.

AT OUR INSTITUTION…

…we define placental lacunae as anechoic spaces within the placenta, surrounded by placental tissue on all sides and measuring ≥5 mm at their greatest diameter. We utilize color Doppler US to evaluate the presence or absence of blood flow within the lacunae. To optimize visualization of low-velocity blood flow within lacunae, we use bidirectional (high-definition) color Doppler US at ≤5–10 cm/sec, with color filters set at the lowest level and color gain maximized.

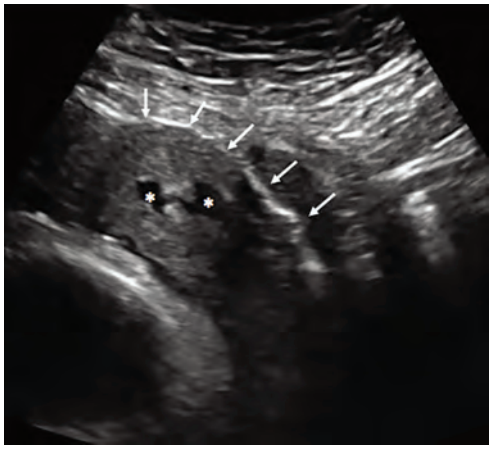
Other US markers of PAS

Retroplacental–myometrial interface

Loss of the normal hypoechoic (clear) retroplacental zone, also referred to as loss of the clear space between placenta and uterus, is another marker of PAS (**FIGURE 5**). This finding corresponds to pathologic loss of the decidua basalis as trophoblastic tissue invades directly through the myometrium.[15] This sonographic finding has been reported to have a detection rate of approximately 93%, with sensitivity of 52% and specificity of 57%, for PAS; the false-positive rate, however, has been in the range of 21% or higher. This marker should *not* be used alone because it is angle-dependent and can be found (as an absent clear zone) in normal anterior placentas.[16]

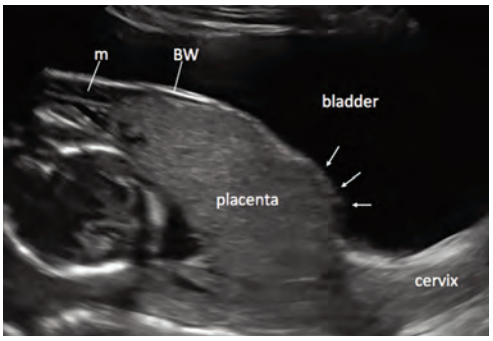
The strength of this US marker is in its negative predictive value, which ranges from 96% to 100%. The presence of a hypoechoic retroplacental clear space that extends the length of the placenta makes PAS unlikely.[17] Of note, the clear zone may appear falsely absent as a result of increased pressure from the US probe.

FIGURE 5 Anterior placenta accreta: Transabdominal US, mid-sagittal plane



A scan at 36 weeks' gestation demonstrates loss of the retroplacental clear zone and placental bulge (arrows), resulting in no measureable retroplacental myometrium. Multiple lacunae are present within the placenta (asterisks).

FIGURE 6 Anterior placenta accreta with distended bladder: Transabdominal US, mid-sagittal plane



On a scan at 18 weeks' gestation, the bladder wall (BW) is hyperechoic and disrupted by a placental bulge (arrows) into the bladder. The retroplacental myometrium (m) is thinned at the level of the placental bulge.

Retroplacental myometrial thickness

Another US finding characteristic of PAS is a retroplacental myometrial thickness of <1 mm (**FIGURE 6**).[15] This finding can result from trophoblastic invasion with minimal intervening myometrium. A thin myometrium also may be due to partial dehiscence (the so-called uterine window) of the uterine wall.[18]

Retroplacental myometrial thickness is difficult to assess because the lower uterine-segment myometrium thins in normal pregnancy as term approaches. This measurement also can be influenced by direct pressure of the US probe and fullness of the maternal bladder.[18] In patients who have had a CD but who do not have PAS, the median myometrial thickness of the lower uterine segment in the third trimester is 2.4 mm.[19]

Thinning of the myometrium in the upper uterine segment always should be of concern. Studies of this marker have reported sensitivity of US ranging from 22% to 100% and specificity from 72% to 100%.[9,20] Given such variability, it is important to standardize the gestational age and sonographic approach for this marker.

Uterovesical interface

Studies also have reported that abnormalities of the uterovesical interface are predictive of PAS. The uterovesical interface is best

FAST TRACK

Retroplacental myometrial thickness is difficult to assess: The lower uterine-segment myometrium thins in normal pregnancy as term approaches

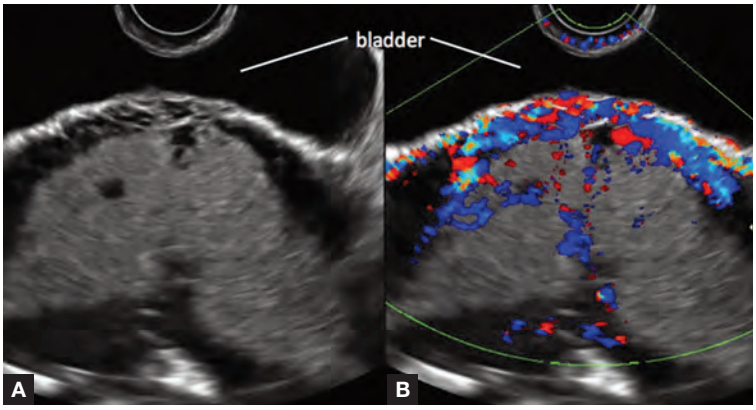
ON OUR US UNIT…

…we optimize transabdominal US imaging of the retroplacental–myometrial interface by applying minimal transducer pressure on the abdomen, minimizing image depth, and magnifying image display. We use linear sweeps to image the entire placenta.

AT OUR INSTITUTION…

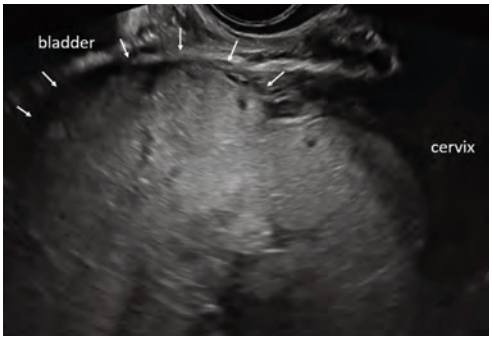
…we typically approach retroplacental myometrial thickness transabdominally by applying minimal transducer pressure on the abdomen, minimizing image depth, and magnifying image display. We measure the myometrium at its thinnest point, taking the measurement perpendicular to the long axis of the wall of the uterus. In the presence of placenta previa or low-lying placenta, we take a transvaginal approach.

FIGURE 7 Placenta accreta: Transvaginal US, transverse view



Views in gray-scale (A) and color Doppler (B) US at 20 weeks' gestation demonstrate increased vascularity of the uterovesical interface.

FIGURE 8 Anterior placenta accreta: Transvaginal US, mid-sagittal plane



A scan at 32 weeks' gestation demonstrates anterior placental bulge with loss of visualization of the retroplacental myometrium (arrows).

evaluated in a sagittal plane containing the lower uterine segment and a partially full bladder in gray-scale and color Doppler US.[15] The normal uterovesical interface appears as a smooth line, without irregularities or increased vascularity on sagittal imaging.

Abnormalities include focal interruption of the hyperechoic bladder wall, bulging of the bladder wall, and increased vascularity, such as varicosities (**FIGURES 5, 6, AND 7**).[15] These findings may be seen as early as the first trimester but are more commonly noted in the second and third trimesters.[7] The authors of a recent meta-analysis concluded that irregularity of the uterovesical interface is the most specific marker for invasive placentation (99.75% confidence interval; range, 99.5% to 99.9%).[13]

AT OUR INSTITUTION…

…we evaluate the uterovesical interface on transvaginal gray-scale and color Doppler US in a midline sagittal view, in which the bladder wall is seen as a hyperechoic band between the uterine serosa and bladder lumen. We subjectively define irregularity of the posterior bladder wall as disruption of the normally smooth bladder wall. We measure the thinnest portion of the myometrium at the uterovesical interface, perpendicular to the long axis of the wall of the uterus with an empty maternal bladder.

Other US markers and modalities

Other proposed US markers of PAS include placental bulge or focal exophytic mass (**FIGURE 8**). More concerning is disruption of the uterine serosa with placental extension, suggesting an exophytic mass, most commonly into the bladder.[21]

Three-dimensional US. Studies have evaluated the role of 3-dimensional (3D) US for predicting PAS. Application of 3D US in vascular mode has shown promise because it allows for semiquantitative assessment of placental vasculature.[22] Using 3D US to screen for PAS presents drawbacks, however: The technology is not well-standardized and requires significant operator expertise for volume acquisition and manipulation. Prospective studies are needed before 3D US can be applied routinely to screen for and diagnose PAS.

Color Doppler US. As an adjunct to gray-scale US, color Doppler US can be used for making a diagnosis of PAS. Color Doppler US helps differentiate a normal subplacental venous complex with nonpulsatile, low-velocity venous blood flow waveforms from markedly dilated peripheral subplacental vascular channels with pulsatile venous-type flow, which suggests PAS. These vascular channels are often located directly over the cervix. In addition, the observation of bridging vessels

ON OUR US UNIT…

…we apply color Doppler US to the retroplacental–myometrial interface and the uterovesical interface to evaluate for abnormal subplacental and uterovesical hypervascularity, defined subjectively by the presence of striking amount of color Doppler US signals in the placental bed, with numerous, closely packed, tortuous vessels demonstrating multidirectional flow and aliasing artifact.[23]

linking the placenta and bladder with high diastolic arterial blood flow also suggests invasion.[21] In a meta-analysis, overall sensitivity of color Doppler US for the diagnosis of PAS was 91%, with specificity of 87%.[13]

The value of utilizing multiple markers

The accuracy of US diagnosis of PAS is likely improved by using more than 1 sonographic marker. Pilloni and colleagues,[20] in a prospective analysis, found that 81% of cases of confirmed PAS had ≥2 markers and 51% of cases had ≥3 markers.

Several scoring systems have been proposed for making the diagnosis of PAS using combinations of sonographic markers, placental location, and clinical history.[19,24,25] In 2016, Tovbin and colleagues,[25] in a prospective study, evaluated a scoring system that included:

- number of previous CDs
- number of, maximum dimension of, and presence of blood flow in lacunae
- loss of uteroplacental clear zone
- placental location
- hypervascularity of the uterovesical or uteroplacental interface.

Tovbin assigned 1 or 2 points to each criterion. Each sonographic marker was found to be significantly associated with PAS when compared to a high-risk control group. A score of ≥8 was considered "at high risk" and predicted 69% of PAS cases.

Regrettably, no combination of US markers reliably predicts the depth of invasion of the placenta.[26]

TABLE How to report US markers for suspected PAS[23]

Always evaluate and report
• Abnormal placental lacunae
• Bladder-wall interruption
• Focal exophytic mass of placenta extending beyond the serosa
• Gray-scale evaluation of loss of the hypoechoic layer between myometrium and placenta
• Myometrial thinning to <1 mm
• Placental bulge distorting extrauterine organs
Also report when color Doppler US is utilized
• Placental lacunae feeder vessels causing turbulent flow
• Presence of bridging vessels from the placenta crossing the myometrium into adjacent structures
• Subplacental hypervascularity
• Uterovesical hypervascularity
Also document
• Suspicion of parametrial involvement

A standardized approach is needed

To decrease variability and improve the US diagnosis of PAS, it is important to define and standardize the diagnosis of each sonographic marker for PAS.[4] In 2016, the European Working Group on Abnormally Invasive Placenta (EW-AIP) proposed a set of US markers that always should be reported when performing an US examination for suspected abnormal placentation (**TABLE**).[23] Despite this effort by the EW-AIP, ambiguity remains over sonographic definitions of several PAS markers. For example, what determines a placental lacuna on US? And what constitutes an abnormal uterovesical interface? There is a need for a more objective definition of US markers of PAS and a standardized approach to the US examination in at-risk pregnancies.

The Society for Maternal-Fetal Medicine is coordinating a multi-society task force to address the need to define and standardize the US diagnosis of PAS.

Observations on other PAS diagnostic modalities

Magnetic resonance imaging

Adjunctive role. Magnetic resonance imaging (MRI) is often used as an adjunctive

US evaluation of the risk of placenta accreta spectrum: The authors' recommended approach

- Assess a priori risk for the patient before initiating the US exam
- In the presence of a placenta previa, or low-lying placenta, we strongly recommend a transvaginal, in addition to transabdominal, US to further assess for the presence of placenta accreta spectrum (PAS) markers
- Until prospective studies clearly define the diagnostic accuracy of PAS sonographic markers and their performance in high-risk and low-risk pregnancies, we recommend that US findings be reported as a risk profile—that is, high, moderate, and low risk of PAS
- Be especially cautious with patients who are at substantially increased risk for PAS, such as those with placenta previa and prior multiple CDs. In this setting, a low-risk report for PAS only should be provided when *none* of the PAS markers are seen on transabdominal and transvaginal US examinations
- While awaiting national guidelines that 1) standardize the approach to the US examination and 2) define PAS US markers, we encourage US laboratories to develop local protocols to standardize the sonographic evaluation of the placenta and ensure uniform and complete placental assessment

FAST TRACK

Until PAS sonographic markers are clearly defined, report US findings as a risk profile—high, moderate, and low risk of PAS

diagnostic modality in cases of suspected PAS. Several markers for PAS have been described on MRI, including[15]:

- intraplacental T2-weighted dark bands
- abnormal intraplacental vascularity
- heterogeneous intraplacental signal intensity
- focal interruption of the myometrium by the placenta
- uterine bulging.

Based on a recent meta-analysis, overall sensitivity of MRI for detecting PAS is 86% to 95%, with specificity of 80% to 95%. Although this is comparable to the sensitivity and specificity of US,[27] studies of MRI in PAS are smaller and more prone to bias than in studies of US, because MRI typically is used only in patients at highest risk for PAS. Few studies comparing US to MRI for PAS have been performed; all are small and lack statistical power.

Complementary role. MRI can be complementary to US in cases in which the placenta is posterior or located laterally[28] but, importantly, rarely changes decisions about surgical management when used in conjunction with US to assess patients for the diagnosis of PAS. (An exception might lie in the ability of MRI to assess the degree or depth of invasion of the placenta and discerning placenta percreta from placenta accreta.[15])

Enhancement with contrast. Addition of gadolinium-based contrast might improve the ability of MRI to make a diagnosis of PAS, but gadolinium crosses the placenta barrier. Although fetal effects of gadolinium have not been observed, American College of Radiology guidelines recommend avoiding this contrast agent during pregnancy unless absolutely essential.[29]

Specific indications. MRI *without* contrast should be considered 1) when US is inconclusive and 2) to further evaluate a posterior placenta suspicious for invasion, to define the precise topography of extrauterine placental invasion. The additional information offered by MRI might alter surgical planning.[15]

Biomarkers

Multiple serum biomarkers have been proposed to predict PAS in high-risk women. PAS might be associated with increased levels of first-trimester pregnancy-associated plasma protein A, second-trimester maternal serum alpha fetoprotein, and human chorionic gonadotropin, but studies of the utility of these biomarkers have yielded contradictory results.[30,31] Biomarkers are of interest and have significant clinical applicability, but none of the ones identified to date have high sensitivity or specificity for predicting PAS prenatally. Research is ongoing to identify markers of PAS that have sufficient predictive power. ●

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FAST TRACK

Standardization of placental marker definitions and placenta evaluation in at-risk pregnancies are initial steps, and prospective studies are needed to refine and evaluate prenatal diagnosis of PAS by US

SCOTUS RECAP

Abortion, the travel ban, and other top Supreme Court rulings affecting your practice

Many decisions made by SCOTUS in the 2017–2018 term concern you and your patients. With Justice Kennedy retired, and his often deciding vote in 5-4 decisions, case outcomes for the next term may depend largely on the new face of the court.

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

IN THIS ARTICLE

The 2017–2018 term of the Supreme Court of the United States (SCOTUS) was momentous. Justice Anthony Kennedy, who had been the deciding vote in most of the 5 to 4 cases for a generation, announced his retirement as of July 31, 2018. In addition, the Court decided a number of cases of interest to ObGyns. In this article we review some of those cases, as well as consider the future of the Court without Justice Kennedy. In selecting cases, we have given special attention to those in which national medical organizations filed *amicus* briefs. These "amicus curiae" or "friend of the court" briefs are filed by an entity who is not party to a case but wants to provide information or views to the court.

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1. Abortion rulings

The Court decided 2 abortion cases and rejected a request to hear a third.

National Institute of Family and Life Advocates v Becerra

In this case,[1] the Court struck down a California law that required pregnancy crisis centers not offering abortions (generally operated by pro-life groups) to provide special notices to clients.[2]

At stake. These notices would inform clients that California provides free or low-cost services, including abortions, and provide a phone number to call for those services.

There were many *amicus* briefs filed in this case, including those by the American College of Obstetricians and Gynecologists (ACOG) and other specialty boards,[3] as well as the American Association of Pro-Life Obstetricians and Gynecologists and other pro-life organizations.[4] ACOG's brief argued that the California-required notice facilitates the goal of allowing women to receive medical services without harmful delay.

Final ruling. The Court held that the law required clinics to engage in speech with which the clinics disagreed (known as "compelled speech"). It also noted that California disclosure requirements were "wildly underinclusive" because they apply only to some clinics. The majority felt that there was no strong state interest in compelling this speech because there were other alternatives for the state to provide information about the availability of abortion and other services. The Court found that the clinics were likely to succeed on the merits of their claims of a First Amendment (free speech) violation.

Right to abortion for illegal immigrants in custody

A very unusual abortion case involved "Jane Doe," a minor who was at 8 weeks' gestation when she illegally crossed the border into the United States.[5] She was placed in a federally-funded shelter where she requested an abortion. The facility denied that request.

At stake. Legal argument ensued about releasing her to another facility for an abortion, as the argument was made that pregnant minors who are apprehended crossing into the United States illegally and placed into the custody of federal officials should have abortion access. A lower Court of Appeals ruled against the Trump Administration's policy of denying abortions to undocumented minors in federal custody. During the process of the federal government taking the case to the Supreme Court, the attorneys for Doe moved appointments around and, without notice, the abortion was performed. Government attorneys said that Doe's attorneys made "what appear to be material misrepresentations and omissions" designed to "thwart [the Supreme Court's] review" of the case.[5] The government requested that the Court vacate the order of the Court of Appeals so that it could not be used as precedent.

Final ruling. The Court granted the governments request to vacate the lower court's order because the minor was no longer pregnant and the order was therefore moot. The basic issue in this case (the right of in-custody minors to access abortions) remains unresolved. It is likely to appear before the Court in the future.

Access to medical abortions

An Arkansas law requires that a physician administering medical abortions contract with a physician who has admitting privileges at a hospital (a "contracted physician").

At stake. Planned Parenthood filed suit challenging the requirement as unnecessary and harmful because it would result in the closure of 2 of the 3 abortion providers in Arkansas. ACOG filed an *amicus* brief urging the Supreme Court to consider the case.[6] (Technically this was a petition for a Writ of Certiorari, the procedure by which the Court accepts cases. It accepts only about 1% of applications.) ACOG argued that there was no medical reason for the contracted physician requirement, and noted the harm it would do to women who would not have access to abortions.

Final ruling. On May 29, 2018, the Court declined to hear the case. This case is still active in the lower courts and may eventually return to the Supreme Court.

2. The patent system

The medical profession depends on the patent system to encourage the discovery of new patents efficiently and effectively. In 2012, Congress passed the America Invents Act[7] that authorizes a petition by anyone other than the patent holder to the Patent and Trademark Office (PTO) for an "*inter partes* review" to assess a challenge to the patent's legitimacy. If the PTO determines that there may be merit to the claim, the Patent Trial and Appeal Board undertakes a trial-like review process that may validate, invalidate, or amend the patent. The Board's decision is subject to appellate court review.

At stake. This term, the *inter partes* review was challenged as unconstitutional on technical bases.[8]

FAST TRACK

In NIFLA v Becerra, the Supreme Court ruled that pregnancy crisis centers in California could not be compelled to provide women with information regarding state-provided services, including abortion

CONTINUED ON PAGE 46

CONTINUED FROM PAGE 45

Final ruling. The Court rejected this claim and approved the current administrative *inter partes* review process. The Court determined that once the Patent Office takes a petition challenging a patent, it must decide *all* of the claims against the patent, not pick and choose which elements of the challenge to evaluate.[9] The Court's decision upheld patent-review reform, but will require the Patent Office to tweak its procedures.

3. The travel ban

ACOG, the American Medical Association (AMA), the Association of American Medical Colleges, and more than 30 other health care and specialty associations filed an *amicus* brief regarding one of the most anticipated cases of the term—the "travel ban."[10]

At stake. The essential argument of these organizations was that the US health care system depends on professionals from other countries. An efficient and fair immigration program is, therefore, important to advance the nation's "health security." During the 2016–2017 term, the Court considered but then removed the issue from its calendar when the Trump Administration issued a revised travel ban.[11]

In September 2017, President Trump's proclamation imposed a range of entry restrictions on the citizens of 8 countries, most (but not all) of which are predominantly Muslim. The government indicated that, in a study by Homeland Security and the State Department, these countries were identified as having especially deficient information-sharing practices and presented national security concerns. *Trump v Hawaii*[12] challenged this proclamation.

Final ruling. The majority of the Court upheld the travel ban. For the 5-Justice majority led by Chief Justice Roberts, the case came down to 3 things:

1. The Constitution and the laws passed by Congress of necessity give the President great authority to engage in foreign policy, including policies regarding entry into the country.
2. The courts are very reluctant to get into the substance of foreign affairs—they are not equipped to know in detail what the facts are, and things change very fast.
3. If courts start tinkering with foreign policy and things turn bad, it will appear that the courts are to blame and were interfering in an area about which they are not competent.

FAST TRACK

When upholding the travel ban, the Supreme Court majority declined to tinker with foreign policy

4. Did a credit card case add risk to health insurance markets?

It was just a credit card case, but one in which the AMA saw a real risk to regulation of the health insurance markets.

At stake. Technically, *Ohio v American Express* concerned a claim that American Express (AmEx) violated antitrust laws when it prohibited merchants taking its credit card from "steering" customers to cards with lower fees.[13] AmEx maintained that, because credit cards were a special kind of "2-sided" market (connecting merchants on one side and customers on the other), antitrust laws should not be strictly enforced.

The AMA noticed that special rules regarding 2-sided markets might apply to health insurance, and it submitted an *amicus* brief[14] that noted: "dominant health insurance networks … have imposed and could further impose rules or effectively erect barriers that prohibit physicians from referring patients to certain specialists, particularly out-of-network specialists, for innovative and even necessary medical tests."[14] It concluded that the antitrust rule AmEx was suggesting would make it nearly impossible to challenge these unfair provisions in health insurance arrangements.

Final ruling. The Court, however, accepted the AmEx position, making it very difficult to develop an antitrust case against 2-sided markets. It remains to be seen the degree to which the AMA concern about health insurance markets will be realized.

5. Gay wedding and a bakeshop

At stake. In *Masterpiece Cakeshop v Colorado*, a cakemaker declined to design a cake for a gay wedding and had been disciplined under Colorado law for discriminating against the couple based on sexual orientation.[15]

Final ruling. The Court, however, found that the Colorado regulators had, ironically, shown such religious animus in the way they treated the baker that the regulators themselves had discriminated on the basis of religion. As a result, the Court reversed the sanctions against the baker.

This decision was fairly narrow. It does not, for example, stand for the proposition that there may be a general religious exception to antidiscrimination laws. The question of broader religious or free-speech objections to antidiscrimination laws remains for another time.

***Amicus* brief.** It was interesting that the American College of Pediatricians, American Association of Pro-Life Obstetricians and Gynecologists, and others, filed an *amicus* brief to report with concern the "demands that individual medical professionals *must* perform, assist with, or facilitate abortions, without regard to the teachings of their own faiths, consciences, and convictions."[16] The brief also noted that "issues in the present case implicate the fundamental rights of health care professionals, and to respectfully urge that the Court should by no means permit any weakening or qualification of well-established protections against compelled speech, and of free exercise" of religion.[16]

Clues to the future

During the term that ran from October 2, 2017, through June 27, 2018, the Court issued 72 decisions. An unusually high proportion of cases (26%; 19 cases) were decided on a 5

FAST TRACK

Although seen as a narrow ruling, the Supreme Court overturned a Colorado decision that found a baker discriminated against a gay couple

Other interesting decisions of the 2017–2018 SCOTUS term

Arbitration. The Court upheld, as it has in most recent terms, another arbitration agreement.[1] This case concerned an employment agreement in which employees consented to submit to arbitration rather than file lawsuits and not use class action claims.

Search of cell-phone location. Cell phones, whenever turned on, connect with cell towers that record the phone's location several times a minute. Cell companies store this information, creating a virtual map of where the owner is at all times. The Federal Bureau of Investigation asked a cell company for location information for several people during a 127-day period in which robberies were committed.[2] The Court held that the search was illegal in the absence of a warrant.

Public employee unions. The Court held that agency (fair share) fees, in which public employees who are not union members can be required to pay dues for the bargaining and grievance activities (from which they generally benefit), violate the First Amendment. The majority held that forcing public employees to pay fees to unions requires the employees, through those fees, to engage in political activities with which they disagree.[3] This is a form of compelled speech, which the Court found violates the First Amendment. Health care professionals who are public employees in positions that have union representation will probably have the opportunity to opt out of agency agreements.

Internet sales tax. The Court permitted states to charge sales tax on out-of-state Internet purchases.[4] In doing so, a state may require out-of-state companies to collect taxes on sales to its residents.

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1. Epic Systems Corp. v Lewis, 584 US 16 285 (2018).
2. Carpenter v United States, 585 US 16 402 (2018).
3. Janus v State, County, and Municipal Employees, 585 US 16 1466 (2018).
4. South Dakota v Wayfair, Inc, 585 US 17 494 (2018).

Justice Kennedy's enduring contribution

Justice Anthony Kennedy was the deciding vote in the overwhelming majority of the 5 to 4 decisions in 20 of his 30 years on the Court. The areas in which he had an especially important impact include[1]:

- **Gay rights.** Justice Kennedy wrote the opinions (usually 5 to 4 decisions) in a number of groundbreaking gay-rights cases, including decriminalizing homosexual conduct, striking down the Defense of Marriage Act, and finding that the Constitution requires states to recognize gay marriage.
- **The death penalty.** Justice Kennedy wrote decisions that prohibited states from imposing the death penalty for any crime other than murder, for defendants who were under 18 when they committed the crime, and for defendants with serious developmental disabilities. He expressed reservations about long-term solitary confinement, but did not have a case that allowed him to decide its constitutionality.
- **The First Amendment.** Early in his service on the Court, he held that the First Amendment protected flag burning as a form of speech. He decided many important free-speech and freedom-of-religion cases that have set a standard for protecting those fundamental freedoms.
- **Use of health and social science data.** Justice Kennedy was more open to mental health information and cited it more often than most other Justices.
- **Abortion rights?** Many commentators would add protecting the right to choose to have an abortion to the above list. Justice Kennedy was a central figure in one case that declined to back away from Roe v Wade, and joined a more recent decision that struck down a Texas law that created an undue burden on women seeking abortion. Plus, he also voted to uphold abortion restrictions, such as "partial-birth-abortion laws." So there is a good argument for including abortion rights on the list, although he did not break new ground.

Justice Kennedy as a person

Outside the courtroom, Justice Kennedy is a person of great warmth and compassion. He is a natural teacher and spends a great deal of time with students. When asked how he would like to be remembered, Justice Kennedy once replied, "Somebody who's decent, and honest, and fair, and who's absolutely committed to the proposition that freedom is America's gift to the rest of the world."

I agree with that assessment.

STEVEN R. SMITH, MS, JD

Reference

1. South Dakota v Wayfair, Inc, 585 US (2018).

FAST TRACK

26% of case decisions in 2017–2018 were a 5 to 4 vote, compared with 10% in 2016–2017

to 4 vote. Last term, the rate of 5 to 4 decisions was 10%; the 6-year average was 18%. The unanimous decision rate was 39% this term, compared with 59% last term, and 50% on average.

The rate of 5 to 4 cases provides a clue about the Court's general direction. The number of times each Justice was in the majority in those nineteen 5 to 4 decisions included: Chief Justice Roberts, 17; and Justices Kennedy, 16; Gorsuch, 16; Thomas, 15; and Alito, 15; compared with Justices Ginsburg, 5; Breyer, 4; Sotomayor, 4; and Kagan, 3.

The Court convened on October 1, 2018. At this writing, whether the new term starts with 8 or 9 justices remains a question. President Trump nominated Brett Kavanaugh, JD, to take Justice Kennedy's place on the Court. His professional qualifications and experience appear to make him qualified for a position on the Court, but as we have seen, there are many other elements that go into confirming a Justice's nomination.

Next term, the Court is scheduled to hear cases regarding pharmaceutical liability, double jeopardy, sex-offender registration,

» The Supreme Court opinions described in this article are available at https://www.supremecourt.gov/opinions/slipopinion/18. Background on all cases considered by the Court is available at http://www.scotusblog.com.

expert witnesses, Social Security disability benefits, and the Age Discrimination in Employment Act. There will be at least 3 arbitration cases. Health care and reproductive rights will continue to be an important part of the Court's docket. ●

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4. Brief amici curiae of American Association of Pro-Life Obstetricians & Gynecologists, et al. in National Institute of Family and Life Advocates v Becerra, January 16, 2018.
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12. Trump v Hawaii, 585 US 17 965 (2018).
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15. Masterpiece Cakeshop, Ltd. v Colorado Civil Rights Commission, 584 US 16 111 (2018).
16. Brief amici curiae of American College of Pediatricians, et al. in Masterpiece Cakeshop v Colorado Civil Rights Commission, September 7, 2017.

A Supplement to OBG MANAGEMENT

This supplement is sponsored by Lupin Pharmaceuticals, Inc.

Effective Management and Counseling of Patients with Recurrent Bacterial Vaginosis

Bacterial vaginosis (BV) affects women worldwide and recurrent BV can be a frustrating condition for both patients and providers. In this new supplement, expert Khady Diouf, MD, discusses her treatment approach and suggested counseling for patients with recurrent BV.

This supplement can be found in the June issue of OBG MANAGEMENT and in the Education Center at the OBG MANAGEMENT website, **https://www.mdedge.com/obgyn/education-center.**

INDEX OF ADVERTISERS

Hemorrhage; bladder laceration during hysterectomy

A 46-YEAR-OLD WOMAN reported increasingly frequent and painful menstrual periods to her Gyn. Estrogen-progestin contraceptives were relatively contraindicated because of the patient's hypertension. The Gyn performed hysteroscopic resection of a submucosal fibroid, dilation and curettage, and endometrial ablation. He attempted to morcellate the 2-cm fibroid from the anterior wall. Blood loss during surgery was noted to be less than 100 mL.

The patient began to hemorrhage immediately after surgery; nurses informed the Gyn of this multiple times over the next several hours. After 7 hours, the Gyn examined the patient, found that she was in hemorrhagic shock, and advised a hysterectomy was necessary. During surgery, the Gyn lacerated the patient's bladder twice, which required a urologist to repair. Postoperatively, the patient had a stroke, respiratory failure, and kidney failure.

PATIENT'S CLAIM: The Gyn's morcellation technique was negligent. He did not respond to the nurses for 7 hours. If he had responded earlier, she might not have lost her uterus. He was also negligent for injuring the patient's bladder during the second surgery.

PHYSICIAN'S DEFENSE: The case was settled during mediation.

VERDICT: A confidential North Carolina settlement was reached.

Bowel injured during BSO

IN 2013, A 52-YEAR-OLD WOMAN underwent bilateral salpingo-oophorectomy (BSO) performed by a Gyn. Postoperatively, she was found to have a 1.5-cm bowel perforation. After surgical repair, she developed a wound infection and wound breakdown. She was treated with a vacuum-assisted wound closure device. She later developed a ventral hernia and an intra-abdominal abscess leading to a colostomy, which eventually was reversed. At trial, she had a low-output bowel-to-skin fistula and extensive abdominal scarring.

PATIENT'S CLAIM: The surgeon should have known to perform open BSO rather than laparoscopic surgery based on her 3 prior abdominal surgeries that would have left severe adhesions. He caused a perforation and/or thermal injury to the sigmoid colon during the BSO. He should have consulted a general surgeon when encountering the adhesions. The surgeon failed to readmit her on a timely basis for treatment of the suspected bowel injury.

PHYSICIAN'S DEFENSE: The severe adhesions encountered during BSO surgery could not have been predicted; no adhesions were noted during a 2004 surgery. The adhesions precluded procedure completion. He attempted to lyse the adhesions to create a visual field for removing the ovaries but they could not be visualized. After using a harmonic scalpel for lysis, he inspected the bowel portions that he could see and found no thermal injury or perforation.

VERDICT: An Illinois defense verdict was returned.

Multiple injuries after LVH

A WOMAN WAS FOUND to have a 4-cm uterine fibroid in April 2007. She received medical management.

In May 2008, she reported left lower quadrant pain to her Gyn. A pelvic ultrasound showed an increase in the fibroid's diameter to 5.8 cm. On December 4 she underwent laparoscopic-assisted vaginal hysterectomy (LVH). The Gyn performed intraoperative cystoscopy. The patient was discharged the following day.

Over the next several weeks, the patient experienced urinary tract symptoms that progressed to rust-colored urine and incontinence. On December 31 she was found to have bilateral vesicovaginal fistulas. By early April 2009, urologists had placed ureteral stents on 2 separate occasions and performed 2 bilateral reimplantation procedures. On April 28, 2009, a urologist placed a stent in the right ureter but was unable to place a stent in the left ureter. The right stent was removed prior to another reconstructive surgery on August 18. Two stents were also placed on August 26 and were removed on October 6. She underwent annual ultrasounds that revealed minimal hydronephrosis. Except for urinary frequency, the patient's symptoms had subsided by trial.

PATIENT'S CLAIM: The Gyn fell below the standard of care during the LVH when he negligently cauterized and/or burned the patient's ureters.

PHYSICIAN'S DEFENSE: The Gyn denied negligence. She argued that, following the cystoscopy, both of the patient's ureteral orifices discharged indigo carmine–stained urine, an indication that there was no injury to the ureters.

VERDICT: A Nevada defense verdict was returned. ●

These cases were selected by the editors of OBG MANAGEMENT *from* Medical Malpractice Verdicts, Settlements, & Experts, *with permission of the editor, Lewis Laska. The information available to the editors about the cases presented here is sometimes incomplete. Moreover, the cases may or may not have merit. Nevertheless, these cases represent the types of clinical situations that typically result in litigation and are meant to illustrate nationwide variation in jury verdicts and awards.*

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