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32-PAGE SECTION
SURGICAL TECHNOLOGY

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ADVANSTAR MEDICAL COMMUNICATIONS GROUP

Your ACA questions—*answered*

IUGR: How to detect & manage

Danielle L. Tate, MD, and Giancarlo Mari, MD

WILL YOU BE AT AAGL?

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OCTOBER 2013 | VOLUME 58, NUMBER 10

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Indication

BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes).

Limitations of Use

- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss, including prescription drugs (eg, phentermine), over-the-counter drugs, and herbal preparations, have not been established.
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

Important Safety Information

Contraindication

- BELVIQ should not be taken during pregnancy or by women who are planning to become pregnant.

Warnings and Precautions

- BELVIQ is a serotonergic drug. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors, tricyclic antidepressants, bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists,

NEW in chronic weight management

Make weight loss matter

Introducing BELVIQ®, the first and only selective 5-HT_{2C} receptor agonist for chronic weight management[1,2]

- Prescription therapy for use in conjunction with a reduced-calorie diet and increased physical activity[1]
- Novel mechanism of action believed to promote satiety. The exact mechanism of action is not known[1,2]

Visit **BELVIQhcp.com** for information and offers.

particularly when used in combination. Patients should be monitored for the emergence of serotonin syndrome symptoms or NMS-like reactions, including agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, diarrhea, and muscle rigidity. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

- Patients should not take BELVIQ in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking BELVIQ and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients were symptomatic. BELVIQ should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of BELVIQ should be considered.
- Impairment in attention, memory, somnolence, confusion, and fatigue, have been reported in patients taking BELVIQ. Patients should not drive a car or operate heavy machinery until they know how BELVIQ affects them.
- The recommended dose of 10 mg twice daily should not be exceeded, as higher doses may cause euphoria, hallucination, and dissociation. Monitor patients for the development or worsening of depression, suicidal thoughts or behaviors, and/or any changes in mood. Discontinue BELVIQ in patients who develop suicidal thoughts or behaviors.
- Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus who are being treated with antidiabetic medications, so measurement of blood sugar levels before and during treatment with BELVIQ is recommended. Decreases in doses of antidiabetic medications or changes in medication regimen should be considered.
- Men who experience priapism should immediately discontinue BELVIQ and seek emergency medical attention. BELVIQ should be used with caution with erectile dysfunction medications. BELVIQ should be used with caution in men who have conditions that might predispose them to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie's disease).
- Because BELVIQ may cause a slow heartbeat, it should be used with caution in patients with a history of bradycardia or heart block greater than first degree.
- Consider monitoring for CBC changes, prolactin excess, and pulmonary hypertension.

Most Common Adverse Reactions

- In patients without diabetes: headache (17%), dizziness (9%), fatigue (7%), nausea (8%), dry mouth (5%), and constipation (6%).
- In patients with diabetes: hypoglycemia (29%), headache (15%), back pain (12%), cough (8%), and fatigue (7%).

Nursing Mothers

- BELVIQ should not be taken by women who are nursing.

BELVIQ is a federally controlled substance (CIV) because it may be abused or lead to dependence.

Please see Brief Summary of Prescribing Information and references on adjacent pages.

BELVIQ® (lorcaserin HCl) CIV

BELVIQ®
(lorcaserin HCl) CIV

BRIEF SUMMARY:
For prescribing information, see package insert.

INDICATIONS AND USAGE
BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:
- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

Limitations of Use:
- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

DOSAGE AND ADMINISTRATION
The recommended dose of BELVIQ is 10 mg administered orally twice daily. Do not exceed recommended dose. BELVIQ can be taken with or without food. Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

CONTRAINDICATION
- Pregnancy

WARNINGS AND PRECAUTIONS
Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions. BELVIQ is a serotonergic drug. The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination.
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.
The safety of BELVIQ when coadministered with other serotonergic or antidopaminergic agents, including antipsychotics, or drugs that impair metabolism of serotonin, including MAOIs, has not been systematically evaluated and has not been established.
If concomitant administration of BELVIQ with an agent that affects the serotonergic neurotransmitter system is clinically warranted, extreme caution and careful observation of the patient is advised, particularly during treatment initiation and dose increases. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.
Valvular Heart Disease. Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took serotonergic drugs with 5-HT$_{2B}$ receptor agonist activity. The etiology of the regurgitant valvular disease is thought to be activation of 5-HT$_{2B}$ receptors on cardiac interstitial cells. At therapeutic concentrations, BELVIQ is selective for 5-HT$_{2C}$ receptors as compared to 5-HT$_{2B}$ receptors. In clinical trials of 1-year duration, 2.4% of patients receiving BELVIQ and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation at one year (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation): none of these patients was symptomatic.
BELVIQ has not been studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease. Preliminary data suggest that 5HT$_{2B}$ receptors may be overexpressed in congestive heart failure. Therefore, BELVIQ should be used with caution in patients with congestive heart failure.
BELVIQ should not be used in combination with serotonergic and dopaminergic drugs that are potent 5-HT$_{2B}$ receptor agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline).
Patients who develop signs or symptoms of valvular heart disease, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur while being treated with BELVIQ should be evaluated and discontinuation of BELVIQ should be considered.
Cognitive Impairment. In clinical trials of at least one year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with BELVIQ and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with BELVIQ in clinical trials included confusion, somnolence, and fatigue.
Since BELVIQ has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BELVIQ therapy does not affect them adversely.
Psychiatric Disorders. Events of euphoria, hallucination, and dissociation were seen with BELVIQ at supratherapeutic doses in short-term studies. In clinical trials of at least 1-year in duration, 6 patients (0.2%) treated with BELVIQ developed euphoria, as compared with 1 patient (<0.1%) treated with placebo. Doses of BELVIQ should not exceed 10 mg twice a day.
Some drugs that target the central nervous system have been associated with depression or suicidal ideation. Patients treated with BELVIQ should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue BELVIQ in patients who experience suicidal thoughts or behaviors.
Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy. Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas); hypoglycemia was observed in clinical trials with BELVIQ. BELVIQ has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting BELVIQ and during BELVIQ treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for anti-diabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting BELVIQ, appropriate changes should be made to the anti-diabetic drug regimen.
Priapism. Priapism (painful erections greater than 6 hours in duration) is a potential effect of 5-HT$_{2C}$ receptor agonism.
If not treated promptly, priapism can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.
BELVIQ should be used with caution in men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease). There is limited experience with the combination of BELVIQ and medication indicated for erectile dysfunction (e.g., phosphodiesterase type 5 inhibitors). Therefore, the combination of BELVIQ and these medications should be used with caution.
Heart Rate Decreases. In clinical trials of at least 1-year in duration, the mean change in heart rate (HR) was -1.2 beats per minute (bpm) in BELVIQ and -0.4 bpm in placebo-treated patients without diabetes and -2.0 beats per minute (bpm) in BELVIQ and -0.4 bpm in placebo-treated patients with type 2 diabetes. The incidence of HR less than 50 bpm was 5.3% in BELVIQ and 3.2% in placebo-treated patients without diabetes and 3.6% in BELVIQ and 2.0% in placebo-treated patients with type 2 diabetes. In the combined population, adverse reactions of bradycardia occurred in 0.3% of BELVIQ and 0.1% of placebo-treated patients. Use with caution in patients with bradycardia or a history of heart block greater than first degree.
Hematological Changes. In clinical trials of at least one year in duration, adverse reactions of decreases in white blood cell count (including leukopenia, lymphopenia, neutropenia, and decreased white cell count) were reported in 0.4% of patients treated with BELVIQ as compared to 0.2% of patients treated with placebo. Adverse reactions of decreases in red blood cell count (including anemia and decreases in hemoglobin and hematocrit) were reported by 1.3% of patients treated with BELVIQ as compared to 1.2% treated with placebo. Consider periodic monitoring of complete blood count during treatment with BELVIQ.
Prolactin Elevation. Lorcaserin moderately elevates prolactin levels. In a subset of placebo-controlled clinical trials of at least one year in duration, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, measured both before and 2 hours after dosing, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively. Prolactin should be measured when symptoms and signs of prolactin excess are suspected (e.g., galactorrhea, gynecomastia). There was one patient treated with BELVIQ who developed a prolactinoma during the trial. The relationship of BELVIQ to the prolactinoma in this patient is unknown.
Pulmonary Hypertension. Certain centrally-acting weight loss agents that act on the serotonin system have been associated with pulmonary hypertension, a rare but lethal disease. Because of the low incidence of this disease, the clinical trial experience with BELVIQ is inadequate to determine if BELVIQ increases the risk for pulmonary hypertension.

ADVERSE REACTIONS
Clinical Trials Experience. In the BELVIQ placebo-controlled clinical database of trials of at least one year in duration, of 6888 patients (3451 BELVIQ vs. 3437 placebo; age range 18-66 years, 79.3% women, 66.6% Caucasians, 19.2% Blacks, 11.8% Hispanics, 2.4% other, 7.4% type 2 diabetics), a total of 1969 patients were exposed to BELVIQ 10 mg twice daily for 1 year and 426 patients were exposed for 2 years.
In clinical trials of at least one year in duration, 8.6% of patients treated with BELVIQ prematurely discontinued treatment due to adverse reactions, compared with 6.7% of placebo-treated patients. The most common adverse reactions leading to discontinuation more often among BELVIQ treated patients than placebo were headache (1.3% vs. 0.8%), depression (0.9% vs. 0.5%) and dizziness (0.7% vs. 0.2%).

Most Common Adverse Reactions

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 practice.
The most common adverse reactions for non-diabetic patients (greater than 5% and more commonly than placebo) treated with BELVIQ compared to placebo were headache, dizziness, fatigue, nausea, dry mouth, and constipation. The most common adverse reactions for diabetic patients were hypoglycemia, headache, back pain, cough, and fatigue. Adverse reactions that were reported by greater than or equal to 2% of patients and were more frequently reported by patients taking BELVIQ compared to placebo are summarized in Table 1 (non-diabetic subjects) and Table 2 (subjects with type 2 diabetes mellitus).

Table 1. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients without Diabetes Mellitus

	Number of Patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=3195**	**Placebo N=3185**
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders And Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections And Infestations		
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin And Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

Table 2. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients with Type 2 Diabetes Mellitus

	Number of Patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=256**	**Placebo N=252**
Gastrointestinal Disorders		
Nausea	24 (9.4)	20 (7.9)
Toothache	7 (2.7)	0

(Table continues)

Table 2. (cont'd.)

Adverse Reaction	Number of Patients (%)	
	BELVIQ 10 mg BID N=256	Placebo N=252
General Disorders And Administration Site Conditions		
Fatigue	19 (7.4)	10 (4.0)
Peripheral edema	12 (4.7)	6 (2.4)
Immune System Disorders		
Seasonal allergy	8 (3.1)	2 (0.8)
Infections And Infestations		
Nasopharyngitis	29 (11.3)	25 (9.9)
Urinary tract infection	23 (9.0)	15 (6.0)
Gastroenteritis	8 (3.1)	5 (2.0)
Metabolism And Nutrition Disorders		
Hypoglycemia	75 (29.3)	53 (21.0)
Worsening of diabetes mellitus	7 (2.7)	2 (0.8)
Decreased appetite	6 (2.3)	1 (0.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	30 (11.7)	20 (7.9)
Muscle spasms	12 (4.7)	9 (3.6)
Nervous System Disorders		
Headache	37 (14.5)	18 (7.1)
Dizziness	18 (7.0)	16 (6.3)
Psychiatric Disorders		
Anxiety	9 (3.5)	8 (3.2)
Insomnia	9 (3.5)	6 (2.4)
Stress	7 (2.7)	3 (1.2)
Depression	6 (2.3)	5 (2.0)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	21 (8.2)	11 (4.4)
Vascular Disorders		
Hypertension	13 (5.1)	8 (3.2)

Other Adverse Reactions

Serotonin-associated Adverse Reactions. SSRIs, SNRIs, bupropion, tricyclic antidepressants, and MAOIs were excluded from the BELVIQ trials. Triptans and dextromethorphan were permitted: 2% and 15%, respectively, of patients without diabetes and 1% and 12%, respectively, of patients with type 2 diabetes experienced concomitant use at some point during the trials. Two patients treated with BELVIQ in the clinical program experienced a constellation of symptoms and signs consistent with serotonergic excess, including one patient on concomitant dextromethorphan who reported an event of serotonin syndrome. Some symptoms of possible serotonergic etiology that are included in the criteria for serotonin syndrome were reported by patients treated with BELVIQ and placebo during clinical trials of at least 1 year in duration. In both groups, chills were the most frequent of these events (1.0% vs. 0.2%, respectively), followed by tremor (0.3% vs. 0.2%), confusional state (0.2% vs. less than 0.1%), disorientation (0.1% vs. 0.1%) and hyperhidrosis (0.1% vs. 0.2%). Because serotonin syndrome has a very low incidence, an association between BELVIQ and serotonin syndrome cannot be excluded on the basis of clinical trial results.

Hypoglycemia in Patients with Type 2 Diabetes. In a clinical trial of patients with type 2 diabetes mellitus, hypoglycemia requiring the assistance of another person occurred in 4 (1.6%) of BELVIQ-treated patients and in 1 (0.4%) placebo-treated patient. Of these 4 BELVIQ-treated patients, all were concomitantly using a sulfonylurea (with or without metformin). BELVIQ has not been studied in patients taking insulin. Hypoglycemia defined as blood sugar less than or equal to 65 mg/dL and with symptoms occurred in 19 (7.4%) BELVIQ-treated patients and 16 (6.3%) placebo-treated patients.

Cognitive Impairment. In clinical trials of at least 1-year duration, adverse reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) occurred in 2.3% of patients taking BELVIQ and 0.7% of patients taking placebo.

Psychiatric Disorders. Psychiatric disorders leading to hospitalization or drug withdrawal occurred more frequently in patients treated with BELVIQ (2.2%) as compared to placebo (1.1%) in non-diabetic patients.

Euphoria. In short-term studies with healthy individuals, the incidence of euphoric mood following supratherapeutic doses of BELVIQ (40 and 60 mg) was increased as compared to placebo. In clinical trials of at least 1-year duration in obese patients, euphoria was observed in 0.17% of patients taking BELVIQ and 0.03% taking placebo.

Depression and Suicidality. In trials of at least one year in duration, reports of depression/mood problems occurred in 2.6% BELVIQ-treated vs. 2.4% placebo-treated and suicidal ideation occurred in 0.6% BELVIQ-treated vs. 0.4% placebo-treated patients. 1.3% of BELVIQ patients vs. 0.6% of placebo patients discontinued drug due to depression-, mood-, or suicidal ideation-related events.

Laboratory Abnormalities. *Lymphocyte and Neutrophil Counts.* In clinical trials of at least 1-year duration, lymphocyte counts were below the lower limit of normal in 12.2% of patients taking BELVIQ and 9.0% taking placebo, and neutrophil counts were low in 5.6% and 4.3%, respectively. *Hemoglobin.* In clinical trials of at least 1-year duration, 10.4% of patients taking BELVIQ and 9.3% taking placebo had hemoglobin below the lower limit of normal at some point during the trials.

Prolactin. In clinical trials, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively.

Eye Disorders. More patients on BELVIQ reported an eye disorder than patients on placebo in clinical trials of patients without diabetes (4.5% vs. 3.0%) and with type 2 diabetes (6.3% vs. 1.6%). In the population without diabetes, events of blurred vision, dry eye, and visual impairment occurred in BELVIQ-treated patients at an incidence greater than that of placebo. In the population with type 2 diabetes, visual disorders, conjunctival infections, irritations, and inflammations, ocular sensation disorders, and cataract conditions occurred in BELVIQ-treated patients at an incidence greater than placebo.

Echocardiographic Safety Assessments

The possible occurrence of regurgitant cardiac valve disease was prospectively evaluated in 7794 patients in three clinical trials of at least one year in duration, 3451 of whom took BELVIQ 10 mg twice daily. The primary echocardiographic safety parameter was the proportion of patients who developed echocardiographic criteria of mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency from baseline to 1 year. At 1 year, 2.4% of patients who received BELVIQ and 2.0% of patients who received placebo developed valvular regurgitation. The relative risk for valvulopathy with BELVIQ is summarized in Table 3. BELVIQ was not studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease.

Table 3. Incidence of FDA-Defined Valvulopathy at Week 52 by Treatment Group[1]

	Study 1		Study 2		Study 3	
	BELVIQ N=1278	Placebo N=1191	BELVIQ N=1208	Placebo N=1153	BELVIQ N=210	Placebo N=209
FDA-defined Valvulopathy, n (%)	34 (2.7)	28 (2.4)	24 (2.0)	23 (2.0)	6 (2.9)	1 (0.5)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

[1] Patients without valvulopathy at baseline who received study medication and had a post-baseline echocardiogram; ITT-intention-to-treat; LOCF-last observation carried forward.

DRUG INTERACTIONS

Use with Other Agents that Affect Serotonin Pathways. Based on the mechanism of action of BELVIQ and the theoretical potential for serotonin syndrome, use with extreme caution in combination with other drugs that may affect the serotonergic neurotransmitter systems, including, but not limited to, triptans, monoamine oxidase inhibitors (MAOIs, including linezolid, an antibiotic which is a reversible non-selective MAOI), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), dextromethorphan, tricyclic antidepressants (TCAs), bupropion, lithium, tramadol, tryptophan, and St. John's Wort.

Cytochrome P450 (2D6) substrates. Use caution when administering BELVIQ together with drugs that are CYP 2D6 substrates, as BELVIQ can increase exposure of these drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category X.

Risk Summary. BELVIQ is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. Maternal exposure to lorcaserin in late pregnancy in rats resulted in lower body weight in offspring which persisted to adulthood. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Clinical Considerations. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Animal Data. Reproduction studies were performed in pregnant rats and rabbits that were administered lorcaserin during the period of embryofetal organogenesis. Plasma exposures up to 44 and 19 times human exposure in rats and rabbits, respectively, did not reveal evidence of teratogenicity or embryolethality with lorcaserin hydrochloride.

In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21 at 5, 15, and 50mg/kg lorcaserin; pups were indirectly exposed in utero and throughout lactation. The highest dose (~44 times human exposure) resulted in stillborns and lower pup viability. All doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected at any dose.

Nursing Mothers. It is not known whether BELVIQ is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use. The safety and effectiveness of BELVIQ in pediatric patients below the age of 18 have not been established and the use of BELVIQ is not recommended in pediatric patients.

Geriatric Use. In the BELVIQ clinical trials, a total of 135 (2.5%) of the patients were 65 years of age and older. Clinical studies of BELVIQ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Since elderly patients have a higher incidence of renal impairment, use of BELVIQ in the elderly should be made on the basis of renal function. Elderly patients with normal renal function should require no dose adjustment.

Renal Impairment. No dose adjustment of BELVIQ is required in patients with mild renal impairment. Use BELVIQ with caution in patients with moderate renal impairment. Use of BELVIQ in patients with severe renal impairment or end stage renal disease is not recommended.

Hepatic Impairment. Dose adjustment is not required for patients with mild hepatic impairment (Child-Pugh score 5-6) to moderate hepatic impairment (Child-Pugh score 7-9). The effect of severe hepatic impairment on lorcaserin was not evaluated. Use lorcaserin with caution in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance. BELVIQ is listed in Schedule IV of the Controlled Substances Act.

Abuse. In a human abuse potential study in recreational drug abusers, supratherapeutic oral doses of lorcaserin (40 and 60 mg) produced up to two- to six-fold increases on measures of "High", "Good Drug Effects", "Hallucinations" and "Sedation" compared to placebo. These responses were similar to those produced by oral administration of the positive control drugs, zolpidem (15 and 30 mg) and ketamine (100 mg). In this study, the incidence of the adverse reaction of euphoria following lorcaserin administration (40 and 60 mg; 19%) is similar to the incidence following zolpidem administration (13-16%), but less than the incidence following ketamine administration (50%). The duration of euphoria following lorcaserin administration persisted longer (> 9 hours) than that following zolpidem (1.5 hours) or ketamine (2.5 hours) administration.

Overall, in short-term studies with healthy individuals, the rate of euphoria following oral administration of lorcaserin was 16% following 40 mg (n = 11 of 70) and 19% following 60 mg (n = 6 of 31). However, in clinical studies with obese patients with durations of 4 weeks to 2 years, the incidence of euphoria and hallucinations following oral doses of lorcaserin up to 40 mg was low (< 1.0%).

Dependence. There are no data from well-conducted animal or human studies that evaluate whether lorcaserin can induce physical dependence, as evidenced by a withdrawal syndrome. However, the ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at supratherapeutic doses suggests that lorcaserin may produce psychic dependence.

OVERDOSAGE

No experience with overdose of BELVIQ is available. In clinical studies that used doses that were higher than the recommended dose, the most frequent adverse reactions associated with BELVIQ were headache, nausea, abdominal discomfort, and dizziness. Single 40- and 60-mg doses of BELVIQ caused euphoria, altered mood, and hallucination in some subjects. Treatment of overdose should consist of BELVIQ discontinuation and general supportive measures in the management of overdosage. BELVIQ is not eliminated to a therapeutically significant degree by hemodialysis.

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*Morning sickness is a common term for a medical condition called Nausea and Vomiting of Pregnancy.[3]

NVP | NAUSEA AND VOMITING OF PREGNANCY

Indication

Diclegis® is a fixed-dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

Diclegis is contraindicated in women with known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride, or any inactive ingredient in the formulation. Diclegis is also contraindicated in combination with monoamine oxidase inhibitors (MAOIs) as MAOIs intensify and prolong the adverse CNS effects of Diclegis. Use of MAOIs may also prolong and intensify the anticholinergic (drying) effects of antihistamines.

Diclegis may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using Diclegis until cleared to do so by their healthcare provider.

Use of Diclegis is not recommended if a woman is concurrently using CNS depressants, such as alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates, and sleep aids. The combination of Diclegis and CNS depressants could result in severe drowsiness leading to falls or other accidents.

Diclegis has anticholinergic properties and should be used with caution in women who have: (1) asthma, (2) increased intraocular pressure, (3) an eye problem called narrow angle glaucoma, (4) a stomach problem called stenosing peptic ulcer, (5) pyloroduodenal obstruction, or (6) a bladder problem called bladder-neck obstruction.

Fatalities have been reported from doxylamine overdose in children. Children appear to be at a high risk for cardiorespiratory arrest. However, the safety and effectiveness of Diclegis in children under 18 years of age have not been established.

Diclegis is a delayed-release formulation; therefore, signs and symptoms of intoxication may not be apparent immediately. Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, and tachycardia. If you suspect an overdose or seek additional overdose information, you can contact a poison control center at 1-800-222-1222.

The FDA granted Diclegis Pregnancy Category A status, which means that the results of controlled studies have not shown increased risk to an unborn baby during pregnancy.

Women should not breast-feed while using Diclegis because the antihistamine component (doxylamine succinate) in Diclegis can pass into breast milk. Excitement, irritability, and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of Diclegis resulting in worsening of their apnea or respiratory conditions.

Diclegis®

(doxylamine succinate and pyridoxine hydrochloride)
delayed-release tablets 10mg/10mg

To report suspected adverse reactions, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying Brief Summary of the full Prescribing Information on adjacent page.

Tablet(s) shown are not actual size.

References: 1. Diclegis [package insert]. Bryn Mawr, PA: Duchesnay USA, Inc; 2013. **2.** US Department of Health and Human Services. Food and Drug Administration. Labeling. 21 CFR 201.57. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57. Revised April 1, 2013. Accessed August 22, 2013. **3.** ACOG Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 52, April 2004. Nausea and vomiting of pregnancy. *Obstet Gynecol.* 2004;103(4):803-815.

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Rx only

DICLEGIS® (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.
PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

DICLEGIS is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

DOSAGE AND ADMINISTRATION

Initially, take two DICLEGIS delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, take the usual dose of two tablets at bedtime that night then take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately control symptoms on Day 4, continue taking three tablets daily. Otherwise take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).

The maximum recommended dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime) daily.

Take on an empty stomach with a glass of water. Swallow tablets whole. Do not crush, chew, or split DICLEGIS tablets.

Take as a daily prescription and not on an as needed basis. Reassess the woman for continued need for DICLEGIS as her pregnancy progresses.

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

CONTRAINDICATIONS

DICLEGIS is contraindicated in women with any of the following conditions:

- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation
- Monoamine oxidase (MAO) inhibitors intensify and prolong the adverse central nervous system effects of DICLEGIS *(see Drug Interactions)*.

WARNINGS AND PRECAUTIONS

Activities Requiring Mental Alertness

DICLEGIS may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so by their healthcare provider.

DICLEGIS use is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol. The combination may result in severe drowsiness leading to falls or accidents *(see Drug Interactions)*.

Concomitant Medical Conditions

DICLEGIS has anticholinergic properties and, therefore, should be used with caution in women with: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.

Drug Interactions

Use of DICLEGIS is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with DICLEGIS is not recommended.

Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of DICLEGIS may be further delayed and a reduction in absorption may occur when tablets are taken with food. Therefore, DICLEGIS should be taken on an empty stomach with a glass of water *(see Dosage and Administration)*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

- Somnolence *(see Warnings and Precautions)*
- Falls or other accidents resulting from the effect of the combined use of DICLEGIS with CNS depressants including alcohol *(see Warnings and Precautions)*

Clinical Trial 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 and efficacy of DICLEGIS was compared to placebo in a double-blind, randomized, multi-center trial in 261 women with nausea and vomiting of pregnancy. The mean gestational age at enrollment was 9.3 weeks, range 7 to 14 weeks gestation *(see Clinical Studies)*. Adverse reactions for DICLEGIS that occurred at an incidence ≥5 percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1: Number (Percent) of Subjects with ≥ 5 Percent Adverse Reactions in a 15 Day Placebo-Controlled Study of DICLEGIS (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence with DICLEGIS than Placebo are shown)

	DICLEGIS (N = 133)	Placebo (n = 128)
Somnolence	19 (14.3%)	15 (11.7%)

To report suspected adverse reactions, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Postmarketing Experience

The following adverse events, listed alphabetically, have been identified during post-approval use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: dyspnea, palpitation, tachycardia
Ear and labyrinth disorders: vertigo
Eye disorders: vision blurred, visual disturbances
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea
General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise
Immune system disorders: hypersensitivity
Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor hyperactivity
Psychiatric disorders: anxiety, disorientation, insomnia, nightmares
Renal and urinary disorders: dysuria, urinary retention
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculo-papular

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of many epidemiological studies (cohort, case control and meta-analyses) designed to detect possible teratogenicity. A meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991 reported no increased risk for malformations from first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis of 12 cohort and 5 case-control studies published between 1963 and 1985 reported no statistically significant relationships between fetal abnormalities and the first trimester use of the combination doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride.

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

The molecular weight of doxylamine succinate is low enough that passage into breast milk can be expected. Excitement, irritability and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of DICLEGIS resulting in worsening of their apnea or respiratory conditions.

Pyridoxine hydrochloride is excreted into breast milk. There have been no reports of adverse events in infants presumably exposed to pyridoxine hydrochloride through breast milk.

Pediatric Use

The safety and effectiveness of DICLEGIS in children under 18 years of age have not been established.

Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures and cardiorespiratory arrest. Children appear to be at a high risk for cardiorespiratory arrest. A toxic dose for children of more than 1.8 mg/kg has been reported. A 3 year old child died 18 hours after ingesting 1,000 mg doxylamine succinate. However, there is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

OVERDOSAGE

Signs and Symptoms of Overdose

DICLEGIS is a delayed-release formulation, therefore, signs and symptoms of intoxication may not be apparent immediately.

Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia.

At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure and death.

Management of Overdose

If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and symptomatic treatment. For additional information about overdose treatment, call a poison control center (**1-800-222-1222**).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

Inform women to avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so.

Inform women of the importance of not taking DICLEGIS with alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates and sleep aids because somnolence could worsen leading to falls or other accidents.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture. Do not remove desiccant canister from bottle.

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BY **CHARLES J. LOCKWOOD, MD, MHCM**

Medical technology
Do the benefits justify the cost?

We all know that American healthcare technology is expensive. But is it worth it?

This issue of *Contemporary OB/GYN* features a fascinating technology update. I would be remiss if I did not comment on the value added to our healthcare system by new technologies.

Is there a declining marginal value to recent medical advances?

In a recent *New York Times* blog, Princeton University health care economist Professor Uwe Reinhardt noted a paradox of modern US health care: It is both high-value and alarmingly wasteful.[1] How can both statements be true?

There can be no argument that medical advances from penicillin to percutaneous coronary angioplasty have dramatically improved both longevity and quality of life—providing great value to society. However, in an era when every week seems to bring the announcement of another hugely expensive biological therapy or more sophisticated imaging technique, one must ask whether we are seeing the same incremental improvement in quality of life for each incremental dollar spent today that we did 50 years ago.

In other words, are we getting the same "bang" for our healthcare "buck?"

Cutler and colleagues examined this very issue by studying medical spending from 1960 through 2000 and comparing the cost of care to the resultant gains in life expectancy in that period.[2] During those 4 decades, overall lifetime healthcare spending climbed nearly 6-fold, from $14,000 to $83,000 per person. But among Americans 65 years and older, who account for most healthcare costs, spending increased more than 13-fold. So what did we get for our money? The answer seems to be diminishing returns!

> "The real "value" (outcome/cost) of medical advances **appears to be falling.**"

Assuming that 50% of the observed improvement in life expectancy that the authors documented accrued to medical advances, the average cost per year of life gained at age 65 rose from $75,100 between 1960 and 1970 to $145,000 between 1990 and 2000. Thus, the real "value" (outcome/cost) of medical advances appears to be falling. And my guess is that this unfavorable trend has accelerated greatly over the past 13 years.

Reinhardt notes that plotting increases in quality-adjusted life years (QALY) gained versus per capita health care spending generates a parabolic curve. Thus, the rate by which QALY

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> We must assess whether new technology significantly improves quality-adjusted life years **for a reasonable cost.**

increase for a given incremental medical cost rapidly accelerates (efficient care), then slows and levels off (inefficient or potentially wasteful care) and finally begins decreasing (unambiguously wasteful care). Reinhardt contends that compared to the past, today substantial additional costs are incurred for very modest QALY gains. He questions whether this incremental cost is worth it or is wasteful.

Reinhardt also points out that at its extreme, where there is a decline in QALY with increasing costs (unambiguous waste), patient harm results from improper care (eg, unnecessary surgery or imaging). According to the Institute of Medicine, waste attributable to unnecessary services and inefficiently delivered care accounts for close to 14% of total healthcare costs, or about $340 billion per year.[3] Thus, it is incumbent on us to assess new technology from the perspective of its true value to society: whether it significantly improves QALY for a reasonable cost.

Of course, when it's you who may marginally benefit from a new diagnostic test or treatment and if you are not directly paying for its high cost, maintaining this intellectual detachment can be difficult.

To give a concrete example of the "Reinhardt curve" in action and the related moral hazard and economic complexity of moving along the curve from left to right, let's look at 2 examples. When the polio vaccine was introduced 50 years ago, it was quite inexpensive per dose and had an extraordinary public health impact. In fact, even now it costs only $56 per dose.[4] By contrast, today the most expensive prescription drug in the world is Idursulfase, an enzyme replacement therapy for patients with Hunter syndrome, that in 2008 was estimated to cost an average of $491,999 per year.[5]

Technology at the margin in ob/gyn

The first time I saw a robotic hysterectomy, I thought, if this had existed when I was a resident, I never would have become a perinatologist! The images were so clear, hand movements so precise, and ergonomics so improved, that it seemed like a different world. Many people felt the same way. Now, according to the manufacturer of the da Vinci system, more than 2000 hospitals have the machine worldwide and 450,000 procedures were performed in 2012.[6] Indeed, it has the potential to become the great leveler of surgical skills, because one no longer needs to be an expert laparoscopist to perform moderately sophisticated minimally invasive surgery. But does it add value to women's health care?

While most reports comparing traditional laparoscopic to robotic-assisted gynecological surgeries are by subspecialists (eg, gynecologic oncologists), large-scale direct comparisons of the 2 modalities employed for benign gynecological surgery show little advantage to the robot. Pasic and colleagues mined the Premier hospital database to review the records of 36,188 patients who underwent minimally invasive hysterectomy in 358 hospitals.[7]

While the vast majority (95%) of cases were traditional laparoscopic hysterectomies, when compared with those performed with robotic assistance, use of the robot was consistently associated with statistically significant higher per-patient average hospital costs ($9640 [95% CI, $9621 to $9659] vs. $6973 [95% CI, $6959 to $6987]). Furthermore, both inpatient and outpatient surgery times were significantly longer for robot-assisted procedures.

A rather limited Cochrane database analysis concluded that "limited evidence showed that robotic surgery did not benefit women with benign gynaecological disease in effectiveness or in safety. Further well-designed RCTs with complete reported data are required to confirm or refute this conclusion."[8]

Of course, such studies do not measure the potential societal benefits of having many gyn surgeons move directly from laparotomy-based to robotic-assisted hysterectomies, thus avoiding large abdominal incisions, wound breakdowns, thromboembolism, lost work time, etc. Moreover, the value of robotic-assisted

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hysterectomy in morbidly obese patients may also be understated.

On the other hand, the art of vaginal hysterectomy, which confers many of the same advantages as the robot, is slowly being lost. Evidence also exists that the incidence of complications surrounding robotic-assisted hysterectomies is higher than commonly appreciated.

Cooper and associates reviewed various governmental and public device-related complication databases and court records to identify robotic surgery-related complications during a 12-year period and noted that 245 events were reported to the FDA, including 71 deaths and 174 nonfatal injuries, with 5 additional cases identified from other databases.[9]

Take-home message

Robotic-assisted hysterectomy is likely equipoised on the "Reinhardt curve" between a clearly efficient, value-adding medical advance and an inefficient and potentially wasteful procedure. Further studies of unintended potential societal benefits accruing to its use ("positive externalities," in economics-speak) are clearly needed to better define the robot's precise location on the cost-benefit curve.

For example, does it reduce global complication rates by eliminating laparotomies? Does it dramatically reduce adverse outcomes in morbidly obese patients? What are the national economic benefits of the resultant shorter recovery time?

Regardless of the findings of such comparative effectiveness studies, in my opinion, reduced robotic surgery operating costs—due to the introduction of competitors and alternative disruptive innovations—would move it to the left on the Reinhardt curve.

However, the case of robotic-assisted hysterectomy is just one example of the kind of analyses needed to assess the value of new technologies. This type of scrutiny will be increasingly employed by large healthcare systems and insurers as well as by you and your practice partners as healthcare reimbursement moves to global payments and capitation.

Do you really need to buy an office ultrasound with 3-D capabilities? Is remote access to a fetal heart rate tracing needed when your hospital employs "laborists"? Is it worth using the latest anti-ovarian-cancer agent that costs $10,000 per month when, on average, it extends life by only 45 days? And at a more prosaic level: Do you really need to prescribe azithromycin for your patient's head cold? COG

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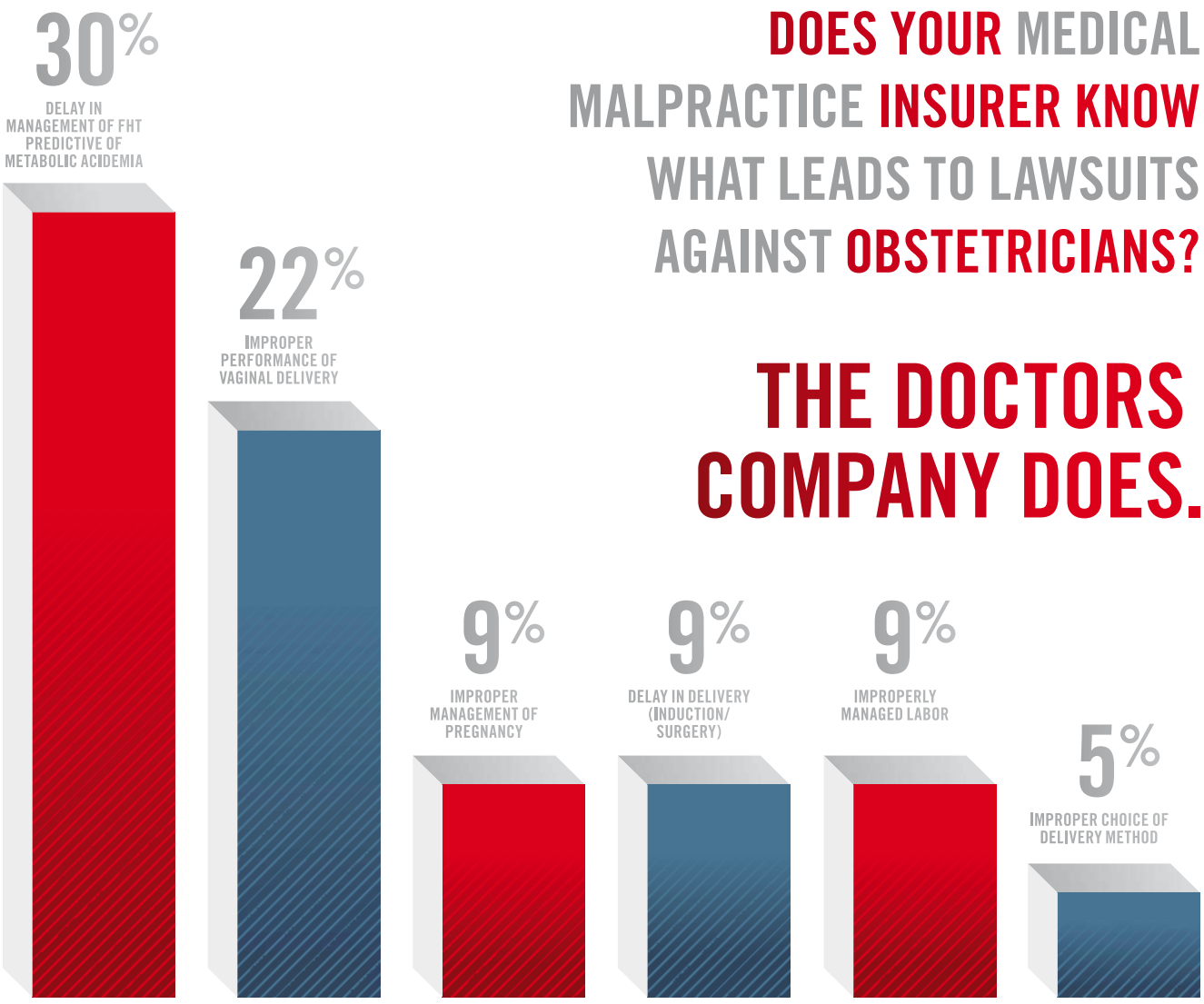

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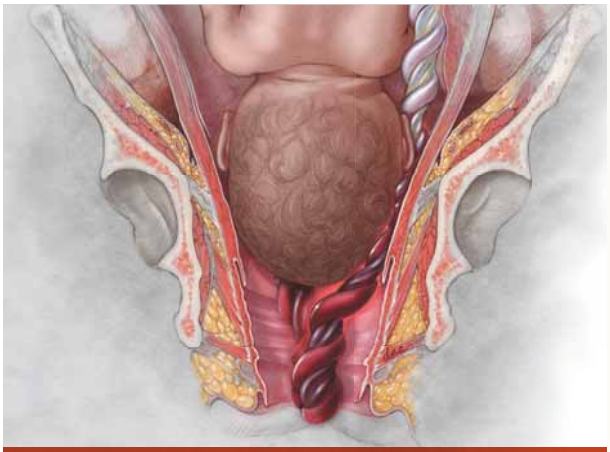

Cord prolapse

An emergency plan

contemporaryobgyn.net/umbilical_cord_prolapse

An umbilical cord prolapse requires swift and sure action. Your initial response can make a difference in maternal and infant outcomes. Authors Bradley D. Holbrook, MD, and Sharon T. Phelan, MD, present a plan of action to help you and your staff prepare for this emergency.

on twitter

A few recent tweets and retweets from and about ContempOBGYN

MHC of Marion County
@MHCMC
Are there racial disparities in infant mortality and prematurity? | Contemporary OB/GYN http://shar.es/igbM8 via @ContempOBGYN

↳ Had your #broccoli today? Compound in it linked to reduced risk of skin #cancer. http://ow.ly/oM5iv via @DermTimesNow #sunscreen

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Serena H Chen
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on facebook

See news, make your opinion known, and read what your colleagues are saying.

Contemporary OB/GYN
September 4

The ob/gyns on our Editorial Board truly go above and beyond in their efforts to improve women's health. Yesterday, Board member Haywood Brown, MD, chaired a meeting of the ACOG National Well-Woman Task Force.

Contemporary OB/GYN
September 8

Ob/gyns, are you ready for ICD-10? In our September issue, Dr. Lockwood explains what you need to do to be prepared. His editorial combines perspective from a leader with resources from industry-leader Medical Economics.

One estimate of the **cost of ICD-10** for a 3-person practice is **$83,000**, rising to $285,000 for a 9- to 10-person practice. These figures are likely to be lower for ob/gyn offices. **My advice is to prepare now.**

digital app

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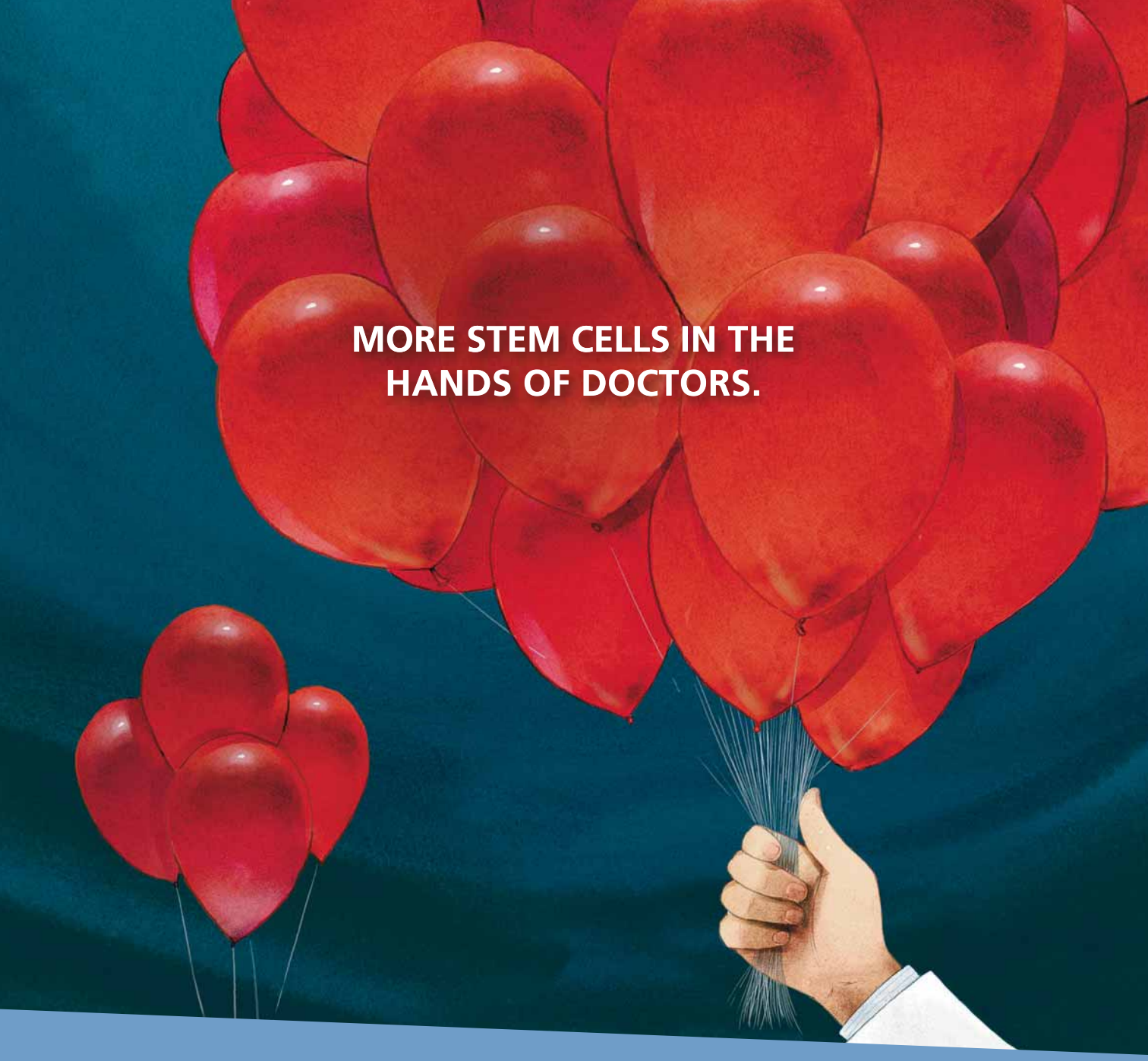

ViaCord delivers more stem cells for greater transplant success.[1,2]

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1. Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med. 1998;339(22):1565-1577. **2.** Kraus M, Foster K, Bridges AR, Walters MC. Cord blood units collected with liquid CPD appear to contain significantly more nucleated and CD34+ cells than units collected with dry heparin. Paper presented at: 51st American Society of Hematology Annual Meeting and Exposition; December 5-8, 2009; New Orleans, LA. Abstract 4227. **3.** Data on file, PerkinElmer, Inc. **4.** Walters MC, Edwards S, Robertson S, Falcon K, Briddell R, Lubin B. Sibling donor cord blood transplantation for hemoglobinopathies. Abstract presented at: 8th Annual International Umbilical Cord Blood Transplantation Symposium; June 3-5, 2010; San Francisco, CA.

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Another study says home births aren't safe

A new study in the *American Journal of Obstetrics and Gynecology* adds even more fuel to the home birth debate. Researchers at New York-Presbyterian/Weill Cornell Medical Center found that infants delivered at home were roughly 10 times more likely to be stillborn and 4 times more likely to develop neonatal seizures or other serious neurologic dysfunction than were their hospital-delivered counterparts.

Researchers used 2007–2010 data from the Centers for Disease Control and Prevention's National Center for Health Statistics on singleton term births (≥ 37 weeks' gestation and a birth weight of ≥ 2500 g). Infants with 5-minute Apgar scores of 0 and seizures or serious neurologic dysfunction were sorted into 4 groups depending on birth setting and birth attendant: hospital physician, hospital midwife, freestanding birth center midwife, and home midwife.

Both home deliveries and freestanding birth center deliveries had a significantly higher risk of a 5-minute Apgar score of 0 than hospital births attended by either a physician or a midwife. A higher risk for neonatal seizures or neurologic dysfunction was also seen with home deliveries and freestanding birth center deliveries.

The researchers concluded that physicians should inform patients of these findings. They also urged physicians to use patient concerns about hospital deliveries to make hospitals more desirable places to deliver.

Tamoxifen 'fogginess' should be taken seriously

Tamoxifen use among some women with breast cancer has been reported to cause mental "fogginess," and researchers have demonstrated that this adverse effect is real, according to an online study published by *The Journal of Neuroscience*.

Tamoxifen, one of the most widely used anti-cancer agents, is toxic to certain cells of the brain and the central nervous system, which may explain the phenomenon of mental "fogginess" that occurs in some women who take it. For some patients the effects wear off over time, but others experience symptoms that can lead to job loss, depression, and other debilitating events, according to study author Mark Noble, PhD.

"Patients aren't always taken seriously when they report these mental side effects, but now we can say this is an organic syndrome to which we have to pay attention ... Despite increasing awareness and research in this area, some people continue to endure short-term memory loss, mental cloudiness, and trouble concentrating," said Noble.

Noble and colleagues isolated the cells in the brain and nervous system that might be harmed by tamoxifen therapy. They found one type of cell that was particularly vulnerable to the drug. After just 2 days of exposure to tamoxifen at levels similar to those someone in treatment would receive, 75% of these cells died.

"The next step was to try to find a medication that could protect these cells from tamoxifen while still allowing the drug to keep its cancer-fighting ability," Noble said. "We only studied drugs that are already approved or in clinical trials. Due to the urgency of these problems, [we] don't have time for 10 to 15 years of drug discovery, so repurposing drugs and finding new uses for them is tremendously important."

New FDA app guidelines

On September 23 the US Food and Drug Administration (FDA) issued final guidance on mobile medical applications, stating that it would regulate only certain medical apps.

Oversight will be given to apps that pose serious risks to patients if they do not work as intended. The FDA determined that all other medical mobile apps pose little risk to consumers if they malfunction. This includes apps that are intended to be used as accessories to medical devices that are already regulated.

Medical mobile apps would be subject to the same regulatory standards as other, more standard medical devices. The FDA has already cleared roughly 100 mobile medical apps in the past year.

The FDA said that it had received more than 130 comments on the guidance, nearly all of which supported the approach.

Indication

Osphena™ (ospemifene) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Select Important Safety Information

Boxed WARNING: Endometrial Cancer and Cardiovascular Disorders

Osphena is an estrogen agonist/antagonist with tissue selective effects. In the endometrium Osphena has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen therapy. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo. Osphena 60 mg had thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

Please see additional Important Safety Information and Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following pages.

Select Important Safety Information

Contraindications

- Osphena should not be used in patients with undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia, active deep vein thrombosis (DVT), pulmonary embolism (PE) or active arterial thromboembolic disease or a history of these conditions
- Women who are or may become pregnant. Osphena may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus

Warnings and Precautions

Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Osphena should not be used in women with severe hepatic impairment as it has not been studied.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

Do not use estrogens or estrogen agonists/antagonists, fluconazole, or rifampin concomitantly with Osphena.

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

The first and only NON-ESTROGEN ORAL treatment for moderate to severe dyspareunia, due to menopause

- **REVERSES** key physiological signs of vulvar and vaginal atrophy (VVA), which include increasing superficial cells, decreasing parabasal cells, and decreasing vaginal pH
- Significantly **IMPROVED** the most bothersome symptom (MBS)* of VVA, which was moderate to severe dyspareunia
- Available in a 60-mg **ORAL** tablet taken once daily with food
- Most common adverse reactions include hot flush, vaginal discharge, muscle spasms, hyperhidrosis, and genital discharge

NLY The **FIRST** FDA-approved estrogen agonist/antagonist for moderate to severe dyspareunia, due to menopause.

New Osphena™
(ospemifene) tablets
60 mg

STUDY DESIGN: Two 12-week, randomized, double-blind, placebo-controlled, parallel-group efficacy studies in 1745 generally healthy postmenopausal women. The first clinical study included 3 treatment groups: Osphena 30 mg (n=282), Osphena 60 mg (n=276), and placebo (n=268). The second clinical study included 2 treatment groups: Osphena 60 mg (n=463) and placebo (n=456). Clinical endpoints for both clinical studies included: a mean change from baseline to Week 12 for percentage of superficial cells on a vaginal smear, percentage of parabasal cells on a vaginal smear, vaginal pH, and most bothersome symptom of VVA (dyspareunia) self-reported by the patient.* A 52-week, randomized, double-blind, placebo-controlled, long-term safety study was also conducted with 2 treatment groups: Osphena 60 mg (n=363) and placebo (n=63).

*MBS was defined as the most bothersome moderate to severe symptom at baseline.

osphena.com

OSPHENA™ (ospemifene) 60 mg tablets
BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions (5.2)*].

Cardiovascular Disorders

There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI) [see *Warnings and Precautions (5.1)*].

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 in placebo [see *Warnings and Precautions (5.1)*]. The incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo [see *Warnings and Precautions (5.1)*]. OSPHENA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: OSPHENA is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS: OSPHENA is contraindicated in women with any of the following conditions:
- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarction (MI)], or a history of these conditions
- OSPHENA is contraindicated in women who are or may become pregnant. OSPHENA may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

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

Stroke
In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per ten thousand women-years). The increase in risk was demonstrated in year 1 and persisted.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women in placebo.

Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

Coronary Heart Disease
In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. In the OSPHENA clinical trials, a single MI occurred in a woman receiving 60 mg of ospemifene.

Venous Thromboembolism
In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per ten thousand women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per ten thousand women-years). The increase in VTE risk was demonstrated during the first 2 years.

In the OSPHENA clinical trials, the incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo. Should a VTE occur or be suspected, OSPHENA should be discontinued immediately.

If feasible, OSPHENA should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms
Endometrial Cancer
OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has agonistic effects. In the OSPHENA clinical trials (60 mg treatment group), no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA treatment groups at a rate of 60.1 per thousand women vs 21.2 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 86.1 per thousand women in OSPHENA vs 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs 1.8 per thousand women for placebo.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. The use of progestins with OSPHENA therapy was not evaluated in the clinical trials.

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

Breast Cancer
OSPHENA 60 mg has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Severe Hepatic Impairment
OSPHENA should not be used in women with severe hepatic impairment [see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
- Cardiovascular Disorders [see *Boxed Warnings, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warnings, Warnings and Precautions (5.2)*]

Clinical Trial 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 practice.

The safety of OSPHENA has been assessed in nine phase 2/3 trials (N=1892) with doses ranging from 5 to 90 mg per day. The duration of treatment in these studies ranged from 6 weeks to 15 months. Most women (N=1370) had a treatment period of at least 12 weeks, 409 had at least 52 weeks (1 year) of exposure.

The incidence rates of thromboembolic and hemorrhagic stroke were 0.72 per thousand women (1 reported case of thromboembolic stroke) and 1.45 per thousand women (2 reported cases of hemorrhagic stroke), respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 1.45 per thousand women in OSPHENA 60 mg treatment group (2 reported cases of DVT) and 1.04 (1 case of DVT) in placebo.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

DRUG INTERACTIONS
OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

Estrogens and estrogen agonist/antagonist
OSPHENA should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of OSPHENA with estrogens and estrogen agonists/antagonists has not been studied.

Fluconazole
Fluconazole, a moderate CYP3A/strong CYP2C9/moderate CYP2C19 inhibitor, should not be used with OSPHENA. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Administration of fluconazole with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Rifampin
Rifampin, a strong CYP3A4/moderate CYP2C9/moderate CYP2C19 inducer, decreases the systemic exposure of ospemifene by 58%. Therefore, coadministration of OSPHENA with drugs such as rifampin which induce CYP3A4, CYP2C9 and/or CYP2C19 activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect [see *Clinical Pharmacology (12.3)*].

Ketoconazole
Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold. Administration of ketoconazole chronically with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Warfarin
Repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10 mg dose of warfarin. No study was conducted with multiple doses of warfarin. The effect of ospemifene on clotting time such as the International Normalized Ratio (INR) or prothrombin time (PT) was not studied [see *Clinical Pharmacology (12.3)*].

Highly Protein-Bound Drugs
Ospemifene is more than 99% bound to serum proteins and might affect the protein binding of other drugs. Use of OSPHENA with other drug products that are highly protein bound may lead to increased exposure of either that drug or ospemifene [see *Clinical Pharmacology (12.3)*].

Multiple Enzyme Inhibition
Coadministration of OSPHENA with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of OSPHENA-related adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic effects: Pregnancy Category X [see *Contraindications (4)*].

Nursing Mothers
It is not known whether OSPHENA is excreted in human breast milk. In a nonclinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma.

Pediatric Use
OSPHENA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use
Of the 1892 OSPHENA-treated women enrolled in the nine phase 2/3 trials of OSPHENA, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

Renal Impairment
The pharmacokinetics of ospemifene in women with severe renal impairment (CrCL<30 mL/min) was similar to those in women with normal renal function [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with renal impairment.

Hepatic Impairment
The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C); therefore, OSPHENA should not be used in women with severe hepatic impairment [see *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

OVERDOSAGE
There is no specific antidote for OSPHENA.

Based on OSPHENA (ospemifene) 60 mg tablets, Prescribing Information 02/2013.

SHIONOGI INC.

SHIONOGI INC.

BY DAWN COLLINS, JD

Careful charting protects ob/gyn in case of infant's death

A 30-YEAR-OLD Illinois physician received prenatal care from an obstetrician for her first pregnancy in 2008. When low amniotic fluid and lagging fetal growth were noted in her third trimester, she was referred to a maternal-fetal medicine (MFM) specialist. The MFM recommended induction of labor, for which the patient was admitted at 39 weeks' gestation.

Labor progressed slowly and the obstetrician attempted to deliver the infant with the assistance of a vacuum device. After 3 unsuccessful vacuum delivery attempts, the obstetrician recommended a cesarean delivery because she did not think the baby would deliver vaginally. The patient did not consent to the cesarean delivery until 2 hours later, after another failed attempt at vacuum delivery.

The infant required resuscitation at birth with a full code for more than 20 minutes. The newborn was determined to be anemic after loss of nearly a third of her blood volume and was diagnosed with a subgaleal hemorrhage and had hypoxic ischemic encephalopathy, disseminated vascular coagulation. At age 3 days, she suffered a myocardial infarction, after which she had no brain activity. At 5 days of age, the infant was removed from life support and died.

An autopsy found possible hypereosinophilic syndrome and indicated it to be a concurrent cause of death.

A lawsuit was filed on behalf of the infant, claiming that the obstetrician should have insisted on a cesarean delivery at the time she first recommended it, and that she failed to fully inform the patient of the risks, benefits, and alternatives to use of the vacuum extractor. The patient said she would not have consented to use of the vacuum if she had known the risks to the infant. The argument also was made that the eosiniphilic infiltration into several organs was due to the resuscitation efforts.

The obstetrician argued that the patient did not consent to the recommended cesarean delivery after the first attempt at vacuum delivery, that the vacuum was used appropriately, and that eosinophilia was the cause of the infant's death.

The verdict

A defense verdict was returned.

Legal perspective

In most malpractice cases involving the use of forceps or vacuum, the issues are the indication for use of a device and the application of the device itself. Occasionally, it is disputed that the injury was caused by the device. In this case, however, the parties stipulated that the bleeding was likely caused by the vacuum device.

The major issue, then, is whether the physician should have "strongly suggested" and then insisted on the cesarean delivery at the time of the first failure of the vacuum. The patient, her husband, and 2 other family members present at the time testified that the obstetrician simply posed the possibility of performing a cesarean delivery. The patient claimed that she wanted what was best for the baby and never refused a cesarean delivery.

The obstetric nurse, however, testified that the patient delayed consenting to a cesarean delivery because she felt the baby was so close to being delivered vaginally. Fortunately, the physician noted in the chart that she recommended cesarean delivery at the first vacuum failure and documented that the patient and her husband were "adamant about vaginal delivery." The physician also informed the patient of exactly what she was writing in the chart.

Failure to timely perform cesarean delivery blamed for ADHD and motor difficulties

A 37-year-old Connecticut woman was at term with her first baby in 2006 when her membranes ruptured and she went to the hospital. She was managed by a nurse-midwife, who called an obstetrician when some bleeding was noted.

On arrival, the obstetrician noted that the patient was completely dilated and decided to attempt vaginal delivery with forceps. She could not place the forceps and made an unsuccessful attempt at vacuum-assisted delivery. Consequently, a cesarean delivery was performed. The newborn received care in the neonatal intensive care unit. Four to 5 years later, the child was diagnosed with attention deficit-hyperactivity disorder (ADHD), and has some motor difficulties, including problems with walking, balance, and coordination.

The woman sued those involved with the delivery, claiming that the obstetrician failed to respond to evidence of fetal distress and inappropriately attempted an operative vaginal delivery, which delayed the emergency cesarean delivery. She claimed that this delay caused the fetus to suffer brain injury that resulted in later difficulties.

The physician and hospital contended there was no evidence of fetal distress and the fetal heart rate (FHR) tracing was stable; the bleeding was not substantial; and the attempt at vaginal delivery took very little time, during which the operating room was prepared.

The verdict

A defense verdict was returned.

Timing of fetal injury disputed

In 2001, a Wisconsin woman received prenatal care from a nurse-midwife. When she was overdue, misoprostol (Cytotec) was given to induce labor. She was admitted to the hospital around 2 pm in active labor and 6-cm dilated. Dilation stopped and the nurse-midwife placed the patient in a birthing tub, but contractions continued to slow, so oxytocin was started.

The patient was not fully dilated until 10:30 pm. Around midnight, the FHR pattern showed accelerations with every contraction. The patient continued to push until 1:30 am, when the FHR was removed and she was again placed in a birthing tub. The nurses auscultated the FHR, which was recorded as normal.

On delivery about 30 minutes later, the infant's heart rate (HR) was 80 beats per minute (bpm). She did not breathe spontaneously and her Apgar scores were 1, 3, 3, and 5. A cord blood gas pH was 7.16. An attending physician was called and arrived about 20 minutes later. The infant was resuscitated, intubated, and transferred to another hospital. She was significantly acidotic, but a computed tomography scan performed at 56 hours of life was read as normal. Magnetic resonance imaging at 9 months was also read as normal. The child suffers from cerebral palsy, requires a walker, and has arm and leg impairments and significant cognitive deficits. She requires 24-hour assistance.

A lawsuit was filed. Although the parties did not dispute that the infant suffered an hypoxic/ischemic injury, they disagreed about when it occurred. The patient claimed the injury occurred during delivery. She argued that the oxytocin use was excessive; the FHR strip was actually recording the mother's HR accelerations while pushing; and that the pH was from the vein, not the artery. The plaintiffs also disputed the normal report from the MRI, which their expert said indicated significant brain injury.

The physician and hospital claimed the injury occurred in utero, prior to delivery. They pointed to the normal pH reading and brain scans.

The verdict

The jury returned a verdict for the child, finding the nurse-midwife 80% at fault and the hospital 20% at fault. They awarded $13.5 million to the child and $100,000 to the patient, and added $100,000 in past medical expenses to the total.

Bowel perforations during laparoscopy

A 48-year-old Arizona woman sued her gynecologist after she underwent laparoscopic surgery for treatment of pelvic pain. The woman claimed that the physician failed to diagnose and repair bowel perforations that occurred during her surgery. When the perforations were diagnosed, she had already developed peritonitis and had a prolonged infection. She also claimed that the initial repair of the perforations failed, requiring a small-bowel resection. She developed short bowel syndrome with chronic diarrhea. In addition, she blamed the antibiotics used to treat her infection for a 90% loss of vestibular function in the bowel.

The physician denied any negligence in performance of the initial laparoscopy. He contended that the perforations might not have been detectable during surgery and they had enlarged by the time of pathology examination. He also argued that the small-bowel resection was necessary because of the erosive effect of fecal material on the bowel after perforation occurred.

The verdict

A defense verdict was returned.

Failure to confirm pregnancy termination alleged

A Maryland woman in her mid-thirties went to a women's health clinic to confirm a pregnancy. Once the pregnancy

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was confirmed, the patient decided to terminate it and was prescribed the drug mifepristone (RU-486). She then had a follow-up exam at the clinic, during which the physician confirmed the termination by physical exam; . no ultrasound (U/S) was performed. The patient contacted the clinic a month later, concerned that she was still pregnant. She later claimed that she was told not to worry and to wait another 8 to 12 weeks before following up. She returned to the clinic when she felt movement and an U/S showed a 21-week gestation with a normal-appearing fetus. At 25 weeks she went into premature labor, delivering a fetus with multiple congenital deformities due to the RU-486. The infant died 40 minutes later.

The woman sued the clinic, alleging negligence in failure to perform an U/S following the use of RU-486, and/or to order a blood test to confirm termination of the pregnancy. Additionally, she claimed that the follow-up appointment should have been with the original physician because the physician she saw had never prescribed the drug and lacked experience with its administration and follow-up. She also alleged negligence in advising her that at 21 weeks' gestation that it was too late for termination, despite the likelihood of the child having multiple birth defects, and claimed pain and suffering for herself and the infant.

The physicians maintained that conducting an U/S to determine if the pregnancy had been terminated was not the standard of care and that the patient assumed the risk of the drug not working when she took the medication. The second physician claimed that he advised the patient to follow up with the original doctor, but the patient denied this to be true.

The verdict

A verdict for the patient and child was returned and $250,000 was awarded.

Ureter injury during emergency hysterectomy

A 34-year-old woman underwent a cesarean delivery in 2007 at a New York hospital. A tubal ligation was attempted after delivery of the infant, but uncontrollable, life-threatening hemorrhaging occurred, requiring hysterectomy. Two days later the patient was diagnosed with hydronephrosis, which led to recognition of a ureter injury. She underwent a nephrostomy and also developed a pulmonary embolism during this hospitalization. Nine months later, she underwent repair of the ureter and insertion of a stent. The stent was removed a few months later and the nephrostomy was then reversed.

The woman sued those involved with the hysterectomy, claiming that it was not performed properly and the initial ureteral injury was not diagnosed in a timely manner. She claimed that prompt diagnosis would have prevented the need for most of the subsequent surgeries she required.

The physicians denied any negligence in performance of the hysterectomy, which was emergently required to save the patient's life, and argued that ureteral injury is a known complication of that procedure.

The verdict

A defense verdict was returned.

Did excessive traction cause Erb's palsy?

In 2001, a New York woman's child was delivered by a nurse-midwife in a hospital. The infant was subsequently diagnosed with Erb's palsy. The woman sued the nurse-midwife and the hospital, claiming that the injury was caused by a failure to properly manage a shoulder dystocia and that the nurse-midwife used excessive traction during delivery.

The nurse-midwife argued that no shoulder dystocia had occurred during delivery and excessive traction was not used. She also contended that the palsy had resolved, with the infant able to raise the arm above the shoulder. The arm's length and reflexes were also not affected.

The verdict

A defense verdict was returned.

Bowel perforation during D&C

A 65-year-old woman underwent a dilation and curettage (D&C) in 2006 to rule out cancer. The procedure was performed by her gynecologist and a general surgeon in a New Jersey hospital. The patient's uterus and small bowel were perforated during the D&C, and she underwent a second procedure to repair the damage.

She sued both physicians, alleging negligence in the performance of the D&C, necessitating the second operation.

The general surgeon settled for a confidential amount prior to trial. The case went to trial against the gynecologist, who denied any negligence and contended that the injuries were known complications of the procedure.

continued on **PAGE 27**

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Who should not use Essure

- Essure is contraindicated in patients who are uncertain about ending fertility, can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus), have previously undergone a tubal ligation, are pregnant or suspect pregnancy, delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure, have an active or recent upper or lower pelvic infection, or have a known allergy to contrast media.
- Patients undergoing immunosuppressive therapy (e.g. systemic corticosteroids or chemotherapy) are discouraged from undergoing the Essure procedure.
- Uterine or fallopian tube anomalies may make it difficult to place Essure inserts.

Please see additional Important Safety Information about Essure on next page.

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Important Safety Information continued

Prescription Only

Caution: Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and Physician Training manual; and have successfully completed the Essure training program, including preceptoring in placement until competency is established, typically 5 cases.

Pregnancy Considerations
- The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test [modified hysterosalpingogram (HSG)] demonstrates bilateral tubal occlusion and satisfactory location of inserts.
- Effectiveness rates for the Essure procedure are based on patients who had bilateral placement. If Essure inserts cannot be placed bilaterally, then the patient should not rely on Essure inserts for contraception.
- Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated.
- Pregnancies (including ectopic pregnancies) have been reported among women with Essure inserts in place. Some of these pregnancies were due to patient non-compliance or incorrect clinician interpretation of the Essure Confirmation Test (modified HSG).

Procedural Considerations
- Perform the Essure procedure during early proliferative phase of the menstrual cycle. Terminate procedure if distension fluid deficit exceeds 1500cc or hysteroscopic time exceeds 20 minutes as it may signal uterine or tubal perforation. Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.
- DO NOT perform the Essure procedure concomitantly with endometrial ablation. Avoid electrosurgery on uterine cornua and proximal fallopian tubes without visualizing inserts.

Nickel Allergy
Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.

MRI Information
The Essure insert was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-05.

Clinical Trial Experience
- Safety and effectiveness of Essure is not established in patients under 21 or over 45 years old, nor in patients who delivered or terminated a pregnancy less than 8-12 weeks before procedure. Women undergoing sterilization at a younger age are at greater risk of regretting their decision.
- The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain, and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain, and dyspareunia.

This product does not protect against HIV infection or other sexually transmitted diseases.

References: 1. World Health Organization Department of Reproductive Health and Research (WHO/RHR) and Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP) INFO project. Family Planning: A Global Handbook for Providers 2011. Baltimore and Geneva: CCP and WHO;165. **2.** Arjona JE, et al. Satisfaction and tolerance with office hysteroscopic tubal sterilization. *Fertil Steril*. 2008;90(4):1182-1186. **3.** Cooper JM. Microinsert nonincisional hysteroscopic sterilization. *Obstet Gynecol*. 2003;102(1):59-67. **4.** Essure ESS305: Instructions for use. 03/2012:1-6. **5.** US Department of Health and Human Services. Women's preventive services guidelines: required health plan coverage guidelines. Health Resources and Services Administration website. http://www.hrsa.gov/womensguidelines/. Accessed September 6, 2013.

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continued from **PAGE 24**

The verdict

A defense verdict was returned.

Delay in delivery results in brain damage

A Massachusetts woman went to the hospital in 2004 with contractions at 40 weeks' gestation. She was admitted and FHR strips were reassuring. When her membranes ruptured, a small amount of meconium was noted. The FHR was still normal. About 2 hours later the nurse and nurse-midwife noted some decelerations of the FHR, but they were not repetitive and the FHR continued to be reactive.

About 30 minutes later, the patient began pushing and the FHR dropped to 90 bpm during the contractions. A second midwife arrived to assist, as the first one was less experienced. The patient was given oxygen , her position was changed, she was given an IV fluid bolus. Thirty minutes later the decelerations became prolonged and in the 80 bpm range, and a "code white" was called twice while a physician was en route.

The attending obstetrician attempted delivery with a vacuum extractor, which was unsuccessful, so an emergency cesarean delivery was performed. The infant's Apgar scores were 2, 3, and 3, with a cord pH of 6.66. She developed seizures within the first few minutes of life. Imaging studies revealed evidence of global hypoxic-ischemic encephalopathy. The child could not walk, talk, or sit unsupported at age 8 years. She has a gastrostomy tube, is cortically blind, and requires seizure medication.

The verdict

A $5 million settlement was reached against the nurse and nurse-midwife.

Failure to test parents for platelet antibodies

A 32-year-old California woman became pregnant with her third child and sought prenatal care at a clinic operated by the federal Department of Health and Human Services. She informed the nurse practitioner at the clinic that she had 2 children who had been diagnosed with low platelets after birth, but who were healthy and had no problems. She was seen at the clinic in 2008 until she was at term. She was then admitted for induction of labor and delivered vaginally.

The infant had Apgar scores of 8 and 8, and the platelets were found to be low at 26,000/L. He was transferred to another hospital the next day, where he was diagnosed with hydrocephalus and neonatal alloimmune thrombocytopenia. The infant suffered a massive intracranial bleed, which caused severe neurological injuries and brain damage. A shunt was placed. The child now has significant cognitive delays, cerebral palsy, and mild developmental delays. Subsequent testing of his parents showed that they had different genotypes for platelet antibodies.

In the lawsuit that followed, the parents claimed that because they had 2 children with low platelets, they should have been tested for platelet antibodies during the pregnancy. They alleged that a prenatal diagnosis of alloimmune thrombocytopenia would have allowed for treatment with gamma globulin, which would have prevented the intracranial hemorrhage and the subsequent neurological injuries.

The verdict

A $4.8 million settlement was reached, paid in the form of $2 million in cash and the purchase of a $2.8 million annuity.

Chorioamnionitis caused infant's brain damage

In 2008, a California woman at term was admitted to a hospital for labor and delivery. Labor was prolonged and a cesarean delivery was promptly performed after fetal distress was recognized. The child had brain damage and is now ventilator-dependent. The patient suffered chorioamnionitis associated with the prolonged labor.

The woman sued those involved with the labor and delivery, alleging negligence in failure to perform the cesarean delivery in a timely manner.

The obstetrician and her group settled for a confidential amount and the matter ultimately went to trial against the hospital. The contention was that the nursing staff was not qualified to read FHR tracings and they failed to alert the attending or on-call physician about the fetal distress. The hospital argued that the brain damage was due to the chorioamnionitis, which could not have been predicted or prevented prior to birth.

The verdict

A defense verdict was returned for the hospital. A post-trial motion is pending. COG

MS COLLINS is an attorney specializing in medical malpractice in Long Beach, California. She welcomes feedback on this column via e-mail to dawncfree@gmail.com.

Detection and surveillance of IUGR

A plan for determining if intrauterine growth restriction is present, then monitoring and delivering when and how it's best for mother and infant.

BY **DANIELLE L TATE, MD, AND GIANCARLO MARI, MD**

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Intrauterine growth restriction (IUGR) refers to the inability of a fetus to achieve full growth potential while in utero. Although IUGR is a common complication of pregnancy, the related terminology and diagnostic criteria are controversial. One reason is that most IUGR studies have not differentiated between constitutionally and pathologically small fetuses. In addition, studies on the pathogenesis of IUGR often assume homogeneity of origin, hampering understanding of underlying mechanisms. The consequence is ambiguity about optimal management of IUGR.

Traditionally, population-based growth curves have been used to define IUGR in the United States, with weight below the 10th percentile for gestational age used as a standard definition. However, adverse outcomes and mortality are increased in infants with birth weights between the 10th and 15th percentile. Conversely, many neonates whose weights are below the 10th percentile are healthy.[1]

Several definitions of IUGR are accepted in different areas of the world. In Europe, an abdominal circumference (AC) below the 10th or the 5th percentile is the preferred diagnostic criteria, as opposed to estimated fetal weight (EFW). Published definitions include: weight at birth <2500 g, EFW <10th percentile, AC <10th percentile, EFW <10th percentile with abnormal Doppler indices in the umbilical artery or middle cerebral artery, and AC <10th percentile with abnormal umbilical artery or middle cerebral artery Doppler studies. Other diagnostic criteria employ the fetus as a control for itself or use customized fetal growth standards.[2,3]

The consequences of in utero growth deficiency do not end at birth or in infancy.[4] Barker and others have described an association between birth weight below the 10th percentile and development later in life of hypertension, hypercholesterolemia, coronary heart disease, impaired glucose tolerance, and diabetes.[4] The growth-restricted fetus represents potential problems for its own future and for society.

Ensuring fetal well-being and determining the optimal timing for delivery of an IUGR fetus is a primary goal of fetal specialists. However, the timing of delivery of these fetuses, especially at less than 32 weeks, is

controversial. Furthermore, the optimal method of fetal testing is debatable; in the United States, the most frequently used test is the biophysical profile, whereas in Europe, cardiotocography is preferred.[5]

Etiologies

IUGR can have several different etiologies, many of which may not be determined until postmortem evaluation. Accurate identification of the cause is important because it may affect future pregnancies.

Genetic factors

Approximately 40% of total birth weight is ascribable to genetic factors, and 60% is due to fetal environmental contributions.[6] Although both parents' genes affect growth, maternal genes have the primary influence on birth weight. Johnstone et al reported that sisters of women with growth-restricted babies tend to have growth-restricted babies as well.[7]

In addition, women who were growth restricted or small for gestational age (SGA) at birth are at increased risk of having an IUGR fetus, and specific maternal genotypic disorders can cause growth restriction, including phenylketonuria and dysmorphic syndromes such as dwarfism. Finally, many chromosomal anomalies have been associated with IUGR. Approximately 50% of fetuses with trisomy 13 or trisomy 18 have fetal growth restriction. In addition, confined placental mosaicism has been associated with growth restriction.[8]

Congenital anomalies

Growth restriction is noted in many fetuses with congenital anomalies, including cardiac malformations (as many as 50% to 80% of fetuses with septal defects), anencephaly, and umbilical artery anomalies, including abnormal cord insertions. Approximately 25% of fetuses with a 2-vessel umbilical cord weigh less than 2500 g at birth.[9] Gastroschisis also is often associated with growth restriction and is present in up to 25% of cases.[10]

Infection

Intrauterine infection underlies 5% to 10% of IUGR.[8] Worldwide, malaria accounts for the majority of infection-related growth restriction. Protozoan infections have been identified as potential causes of IUGR.[11] Viral infectious etiologies include cytomegalovirus, rubella, toxoplasmosis, herpes zoster, human immunodeficiency virus, varicella, and syphilis. To date, there are no specific bacterial infections associated with IUGR, but chorioamnionitis is strongly associated with symmetric growth restriction between 28 and 36 weeks' gestation, and with asymmetric growth restriction after 36 weeks' gestation.[12]

Multiple gestations

Multiple gestations carry a 25% risk of IUGR for twin pregnancies and a 60% risk for higher-order gestations.[13] Monochorionic pregnancies are at an additional risk of discordant fetal growth restriction because of twin-twin transfusion syndrome or unequal placental blood and nutrient sharing.

Maternal nutrition

Studies have shown that severely decreased maternal caloric and protein intake is associated with IUGR, especially when it occurs before 26 weeks' gestation. Maternal-fetal glucose concentration has been shown to increase in growth restriction.[14] Decreases in serum concentrations of zinc and folate have also been associated with growth restriction.[15] The most important "nutrient" deficiency causing IUGR is oxygen. Decreased oxygen content inhibits fetal metabolism, leading to suboptimal growth.[16] Many maternal conditions, including hemoglobinopathies, chronic pulmonary disease, and severe maternal kyphoscoliosis, increase risk of IUGR.

Environmental toxins

Maternal cigarette smoking, excess alcohol ingestion (2 or more drinks daily), and illicit drug use (specifically cocaine abuse) have been associated with IUGR. Cigarette smoking symmetrically decreases birth weight by 135 to 300 g, but if stopped before the third trimester, the adverse effects are reduced.[17] Exposure to certain prescribed medications, such as phenytoin, warfarin, and trimethadione, has been associated with an increased IUGR risk depending on the timing, dosage, and known teratogenic effect.

Placental factors

Poor uteroplacental perfusion as a result of abnormal placentation is the most common placental etiology associated with IUGR, a condition defined as placental insufficiency. However, placental insufficiency may not always be *the cause* of the problem, but rather, the *consequence* of a poorly understood, more global disease process.[18]

The process that triggers the cascade of events that causes placental insufficiency is often unknown.

Placental insufficiency is characterized either by a lack of trophoblast-mediated physiologic change in uterine spiral arteries or by abnormal development of the villous vascular tree.[19] In either case, as fetal oxygen demand increases, oxygen delivery falls below a critical point, and the fetus compensates by redistributing its blood flow from the body to the brain, adrenal glands, and heart.[20] These events can be detected by changes in blood flow Doppler velocity studies,[21, 22] manifested first as an elevated systolic/diastolic (S/D) ratio, then an absence of diastolic velocity, and finally by reversed diastolic velocity in the umbilical artery.[23] Fetal cardiac performance is then compromised, which can be detected by changes in the venous flow to the heart (eg, absence or reversed diastolic flow of the ductus venosus). If all these Doppler abnormalities are present, the fetus is at an increased risk of death.[5, 24-27]

Placental insufficiency is the major placental abnormality seen in IUGR but there are many other placental disorders—including abruption, infarction, hemangioma, chrioangioma, and circumvallate shape—that have been implicated.

Maternal vascular disease

Maternal medical conditions associated with vascular disease have been known to result in fetal growth restriction. These disorders include diabetes, chronic hypertension, pregnancy induced hypertension, advanced age, and morbid obesity.

Detection

Diagnosis by maternal physical examination alone has proven to be inaccurate in up to 50% of cases. A single fundal height measurement at 32 to 34 weeks' gestation has been reported to be approximately 65% to 85% sensitive and 96% specific for detecting the growth-restricted fetus.[8] When IUGR is suspected by maternal fundal height, ultrasound for EFW assessment should be performed using fetal biometry. If the EFW is below the 10th percentile, further sonographic evaluation should be performed, including Doppler flow studies, amniotic fluid assessment, and evaluation for structural abnormalities.

During initial evaluation, it is important to note whether growth restriction is symmetric, asymmetric, or mixed. Intrinsic insults that occur early in pregnancy are likely to result in a symmetric growth restriction. An extrinsic insult occurring later in pregnancy will likely result in asymmetric growth restriction. Every effort to identify an etiology should be undertaken once the diagnosis is made.

Limitations in the categorization of IUGR can be attributed to the routine practice of grouping all growth-restricted fetuses based on fetal weight. An alternative grouping is as follows: 1) "SGA" refers to those small fetuses with no discernible pathology and with normal umbilical artery and middle cerebral artery Doppler results; 2) "growth restricted" refers to small fetuses with recognizable pathology and abnormal Doppler studies; and 3) "idiopathic growth restricted" applies to small fetuses with no discernable pathology or abnormal Doppler studies.[28]

Staging of IUGR has also been proposed.[29] This classification is based on fetal biometry, Doppler cardiovascular changes, amniotic fluid volume, and clinical parameters.[29] In addition, the staging system is applicable to pregnancies at any gestational age. In the proposed staging system:

- Stage 0 includes fetuses with an EFW or an AC <10th percentile. Doppler of the umbilical artery and middle cerebral artery is normal.
- Stage I includes fetuses whose EFW or AC is <10th percentile plus abnormal Doppler flow of the umbilical artery or middle cerebral artery.
- Stage II includes fetuses whose EFW or AC is <10th percentile plus absent or reversed Doppler flow of the umbilical artery.
- Stage III includes fetuses whose EFW or AC is <10th percentile plus absent or reversed Doppler flow of the ductus venosus.
- Based on the amniotic fluid index, the IUGR fetus will be either A (amniotic fluid index [AFI] <5 cm) or B (AFI ≥ 5 cm).

Staging system and management

- Stage 0 SGA fetuses have a good prognosis. They are managed as outpatient with Doppler assessment every 2 weeks. If the Doppler remains normal, delivery is recommended at term. If the Doppler becomes abnormal, these fetuses are managed as Stage I IUGR fetuses.
- Stage I IUGR fetuses have mild growth restriction, and affected mothers without preeclampsia are usually managed as outpatients. Antenatal corticosteroids should be given at time of diagnosis. In these fetuses, twice-weekly antenatal testing is recommended. If the non-stress testing (NST) remains reactive and the AFI remains >5 cm, delivery is recommended at 37 weeks. If the umbilical artery Doppler becomes absent, these fetuses should be managed as Stage II IUGR.

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Reference: 1. Quartette™ [Prescribing Information]. Sellersville, PA: Teva Pharmaceuticals USA, Inc.; 2013.

Quartette™ is indicated for use by females of reproductive age to prevent pregnancy.

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WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke.

The use of combination oral contraceptives is associated with increased risks of several serious side effects, including blood clots, stroke, and heart attack. Some women should not take Quartette™, including women with a high risk of arterial or venous thrombotic diseases, liver tumors (benign or malignant) or liver disease, undiagnosed abnormal uterine bleeding, breast cancer or other estrogen- or progestin-sensitive cancer (now or in the past), or those who could be pregnant.

Thromboembolic Disorders and Other Vascular Problems: Stop Quartette™ if an arterial or deep venous thrombotic event (VTE) occurs. If feasible, stop Quartette™ at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Start Quartette™ no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of VTE is highest during the first year of use of a COC. The greatest risk of VTE is present after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC. Use COCs with caution in women with cardiovascular disease risk factors.

Liver Disease: Discontinue Quartette™ if jaundice develops.

High Blood Pressure: Quartette™ is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease. For women with well-controlled hypertension, monitor blood pressure and stop Quartette™ if blood pressure rises significantly. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use.

Carbohydrate and Lipid Metabolic Effects: Carefully monitor prediabetic and diabetic women who are taking Quartette™. Consider alternative contraception for women with uncontrolled dyslipidemias.

Headache: If a woman taking Quartette™ develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Quartette™ if indicated.

Bleeding Irregularities: If unscheduled bleeding persists or occurs after previously regular cycles on Quartette™, check for causes such as pregnancy or malignancy.

Depression: Carefully observe women with a history of depression and discontinue Quartette™ if depression recurs to a serious degree.

Drug Interactions: Drugs or herbal products that induce certain enzymes, including P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding.

Quartette™ does not protect against HIV infection (AIDS) and other sexually transmitted infections.

Most common adverse reactions (≥2%) in clinical trials: headaches (12.2%), heavy/irregular vaginal bleeding (9.7%), nausea/vomiting (8.8%), acne (5.4%), dysmenorrhea (5.4%), increased weight (4.6%), mood changes (2.9%), anxiety/panic attack (2.4%), breast pain (2.2%), and migraine (2.0%).

Use of Quartette™ provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing the same strength synthetic estrogens and progestins (an additional 9 and 13 weeks of exposure to progestin and estrogen, respectively, per year). Before prescribing Quartette™, consider the occurrence of fewer scheduled menses (4 per year instead of 13 per year) against the occurrence of increased unscheduled bleeding and/or spotting. In clinical trials, unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles.

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BRIEF SUMMARY
of Prescribing Information for
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1 INDICATIONS AND USAGE

Quartette™ is indicated for use by females of reproductive age to prevent pregnancy.

4 CONTRAINDICATIONS

Do not prescribe Quartette to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*.
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*.
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*.
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*.
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*.
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*.
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.3)]*.
  - Have diabetes with vascular disease *[see Warnings and Precautions (5.5)]*.
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.6)]*.
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.7)]*.
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*.
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Quartette if an arterial or deep venous thrombotic event (VTE) occurs. Stop Quartette if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Quartette at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE.

Start Quartette no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COC. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.

Use of Quartette provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing the same strength synthetic estrogens and progestins (an additional 9 and 13 weeks of exposure to progestin and estrogen, respectively, per year). In the clinical trial, three cases of deep vein thrombosis were reported.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), and hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use Quartette in women with acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. Acute disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Quartette if jaundice develops.

Liver Tumors

Quartette is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

5.3 High Blood Pressure

Quartette is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Quartette if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.4 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may also worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

5.5 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Quartette. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.6 Headache

If a woman taking Quartette develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Quartette if indicated. Consider discontinuation of Quartette in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (4)]*.

5.7 Bleeding Irregularities

Bleeding and/or spotting that occurs at any time while taking the first 84 tablets (light pink, pink and purple) of each extended-cycle regimen is considered "unscheduled" bleeding/spotting. Bleeding that occurs during the time a woman takes the seven tablets (yellow) containing 10 mcg of ethinyl estradiol is considered "scheduled" bleeding.

Unscheduled and Scheduled Bleeding and Spotting

Unscheduled (breakthrough) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If unscheduled bleeding persists or occurs after previously regular cycles on Quartette, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC. Before prescribing Quartette, consider the occurrence of fewer scheduled menses (4 per year instead of 13 per year) against the occurrence of increased unscheduled bleeding and/or spotting. A 12-month open-label study of the efficacy of Quartette in preventing pregnancy assessed scheduled and unscheduled bleeding *[see Clinical Studies (14)]* in 3,597 women who completed 34,087 28-day cycles of exposure. A total of 178 (4.9%) of the women discontinued Quartette, at least in part, due to bleeding or spotting.

Scheduled (withdrawal) bleeding and/or spotting remained fairly stable over time, with an average of 3 to 4 days of bleeding and/or spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. Table 1 below presents the number of days with unscheduled bleeding, spotting, and unscheduled bleeding and/or spotting in Treatment Cycles 1 to 4.

Table 1: Number of Unscheduled Bleeding, Spotting and Bleeding and/or Spotting Days per 91-day Cycle

Cycle (N)	Days of Unscheduled Bleeding per 84-Day Interval				Median Days Per Subject-Month
	Mean	Q1	Median	Q3	
1 (3330)	7.2	0	4	10	1.0
2 (2820)	3.3	0	0	4	0.0
3 (2433)	2.5	0	0	3	0.0
4 (2213)	2.2	0	0	2	0.0

Cycle (N)	Days of Unscheduled Spotting per 84-Day Interval				Median Days Per Subject-Month
	Mean	Q1	Median	Q3	
1 (3330)	10.7	2	7	15	1.8
2 (2820)	6.7	0	3	9	0.8
3 (2433)	5.2	0	2	6	0.5
4 (2213)	4.4	0	1	5	0.3
Cycle (N)	**Days of Unscheduled Bleeding and/or Spotting per 84-Day Interval**				**Median Days Per Subject-Month**
	Mean	**Q1**	**Median**	**Q3**	
1 (3330)	17.9	5	14	27	3.5
2 (2820)	10.0	1	5	14	1.3
3 (2433)	7.7	0	3	10	0.8
4 (2213)	6.6	0	3	8	0.8

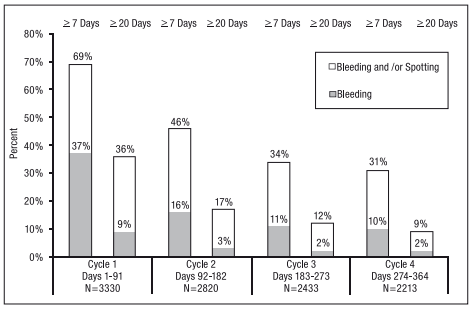
Q1 = Quartile 1: 25% of women had ≤ this number of days of unscheduled bleeding/spotting

Median: 50% of women had ≤ this number of days of unscheduled bleeding/spotting

Q3 = Quartile 3: 75% of women had ≤ this number of days of unscheduled bleeding/spotting

Figure 1 shows the percent of Quartette subjects in the primary clinical trial with ≥ 7 days or ≥ 20 days of unscheduled bleeding and/or spotting, or just unscheduled bleeding, during each 91-day treatment cycle.

Figure 1: Percent of Women Taking Quartette Who Reported Unscheduled Bleeding and/or Spotting



Amenorrhea and Oligomenorrhea

Women who are not pregnant and use Quartette may experience amenorrhea. Based on data from the clinical trial, amenorrhea occurred in approximately 1.9% of women during Cycle 1, 7.7% during Cycle 2, 10.7% during Cycle 3, and 10.1% during Cycle 4 using Quartette. Rule out pregnancy in the event of amenorrhea. Some women may experience amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

5.8 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Discontinue Quartette if pregnancy is confirmed.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.9 Depression

Carefully observe women with a history of depression and discontinue Quartette if depression recurs to a serious degree. Six cases of suicidality (suicide attempts and suicidal behavior) were reported in the clinical trial; several of these cases occurred in women with a psychiatric history.

5.10 Carcinoma of the Breast and Cervix

Quartette is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

5.11 Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.12 Monitoring

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

5.13 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.14 Chloasma

Chloasma may occur with COC use, especially in women with a history of chloasma gravidarum. Advise women who tend to develop chloasma to avoid exposure to the sun or ultraviolet radiation while taking Quartette.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial 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 the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below are from a 12-month, US, open-label study, which enrolled women aged 18-40, of whom 3,597 took at least one dose of Quartette (2,661 woman-years of exposure) *[see Clinical Studies (14)]*.

Adverse Reactions Leading to Study Discontinuation: 13.3% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions (≥ 1% of women) leading to discontinuation were heavy/irregular bleeding (5.0%), mood swings/alteration/affect lability (1.4%), headaches/migraines (1.3%), weight increased (1.3%) and acne (1.0%).

Common Adverse Reactions (≥ 2% of women): headaches (12.2%), heavy/irregular vaginal bleeding (9.7%), nausea/vomiting (8.8%), acne (5.4%), dysmenorrhea (5.4%), weight increased (4.6%), mood changes (depression, depressed mood, crying, major depression, affective disorder, depression suicidal, dysthymic disorder) (2.9%), anxiety/panic attack (2.4%), breast tenderness/pain/discomfort (2.2%), migraine (2.0%).

Serious Adverse Reactions (≥ 2 women): Abortion Spontaneous, Suicide Attempt, Cholecystitis/Cholelithiasis, Deep Vein Thrombosis, Ectopic Pregnancy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of other extended-cycle COCs containing levonorgestrel and ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: abdominal distension, vomiting

General disorders and administration site conditions: chest pain, fatigue, malaise, edema peripheral, pain

Immune system disorders: hypersensitivity reaction

Investigations: blood pressure increased

Musculoskeletal and connective tissue disorders: muscle spasms, pain in extremity

Nervous system disorders: dizziness, loss of consciousness

Psychiatric disorders: insomnia

Reproductive and breast disorders: dysmenorrhea

Respiratory, thoracic and mediastinal disorders: pulmonary embolism, pulmonary thrombosis

Skin and subcutaneous tissue disorders: alopecia

Vascular disorders: thrombosis

7 DRUG INTERACTIONS

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with Quartette.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

- Stage II IUGR fetuses should be managed as inpatients. The fetus should undergo daily antenatal testing with twice-daily NST and daily biophysical profile (BPP). If the NST remains reassuring and the BPP score remains between 6 and 8 of 8, continuation of expectant management is recommended. Antenatal corticosteroids should be given at time of diagnosis. Delivery is recommended at 34 weeks. If the NSTs become non-reassuring or if the BPP score is 4 of 8 on 2 occasions at least 4 hours apart, immediate delivery is recommended. Delivery should be cesarean because fetuses with an absent/reversed flow of the umbilical artery will not tolerate labor induction.
- Stage III IUGR fetuses are managed the same as Stage II except for delivery at 32 weeks' gestation, regardless of gestational age at time of diagnosis. As with Stage I and II, antenatal corticosteroids should be given at time of diagnosis.

The advantage of the above scoring system is its simplicity. Only fetal biometry, sonographic interrogation of 3 fetal vessels, and the AFI are needed. It also allows classification of all small fetuses. If the umbilical artery and middle cerebral artery Doppler is normal, determination of flow velocity waveforms of the ductus venosus is unnecessary because it will be normal as well. The presence of IUGR in the setting of preeclampsia should not deter standard management of preeclampsia.

It is important to note the rate of mortality in the staging system.[29] In a study in which we were able to follow very early IUGR fetuses up to the time of demise (because the patients had declined intervention), no deaths occurred in Stage 0 or Stage I fetuses, whereas the mortality for stage III fetuses was high. The mortality in Stage II IUGR fetuses was intermediate between Stages I and III. Also, studies have shown that fetuses can survive for days or weeks with reversal of flow in the ductus venosus.[29] A recent preliminary study reported that fetuses with reversal of flow in the ductus venosus will not necessarily be acidemic at birth.[30] In addition, the majority of affected pregnancies have an AFI <5 cm before fetal demise occurs.

Categorizing IUGR based on gestational age at time of diagnosis is a novel concept worth mentioning. IUGR fetuses are categorized as: very early IUGR (diagnosed ≤29 weeks), early IUGR (diagnosed between >29 and <34 weeks), and late IUGR (diagnosed >34 weeks). The notion of grouping by gestational age

Two clinical scenarios demonstrating use of IUGR staging

Scenario 1: A fetus with

- **a** EFW <10th percentile
- **b** Normal umbilical artery and middle cerebral artery pulsatility index
- **c** Gestational age: 26 weeks
- **d** AFI =8 cm
- **e** No maternal or fetal pathology

Classification: IUGR stage 0, 26 weeks, idiopathic.

Scenario 2: A fetus with

- **a** EFW <10th percentile
- **b** Abnormal umbilical artery pulsatility index (presence of end diastolic flow velocity)
- **c** Gestational age: 26 weeks
- **d** AFI =8 cm
- **e** Chronic hypertension

Classification: IUGR stage I, 26 weeks, chronic hypertension.

is important because morbidity and mortality differ based on gestational age, even in the absence of complications. To date, this grouping concept has not been studied. However, this introductory discussion may stimulate future studies into this particular classification system.

Unfortunately, it is unclear why there are different types of IUGR but we have postulated 2 hypotheses: a) different causes for the IUGR; and b) the same cause but with different levels of severity.

Timing of delivery

Several studies have provided recommendations for timing of delivery. The loss of the "brain-sparing effect" was initially considered a parameter to guide timing of delivery.[31] Other studies have reported a temporal sequence of Doppler changes preceding the onset of late decelerations.[32] Early Doppler changes occur in all IUGR fetuses, whereas late Doppler changes occur in idiopathic IUGR and in only a few IUGR cases diagnosed in patients with preeclampsia.[33] In idiopathic IUGR, the changes are predictable and occur one after the other. In preeclamptic patients, however, the changes are unpredictable, can occur in a few hours, and in most cases, do not occur because delivery is performed for maternal indication.[33]

Few randomized controlled trials have been performed addressing when to deliver IUGR fetuses. The Growth Restriction Intervention Trial (GRIT) compared 2 management strategies: immediate and delayed delivery in high-risk pregnancies with clinical uncertainty.[34] The results demonstrated that differences in perinatal morbidity and mortality, neurologic outcome 2 years after birth, and long-term outcome were not statistically significant between the 2 groups.[35] However, antenatal testing via BPP and Doppler (with the exception of the umbilical artery) were not used for fetal surveillance in all cases. In addition, the growth-restricted fetuses included in the study represented a heterogeneous population because, in this study, one-fourth of the fetuses had normal umbilical artery flow velocity waveforms, indicating they may have simply been SGA.

A second randomized trial, the Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT), compared composite neonatal morbidity and mortality of IUGR pregnancies beyond 36 weeks wiht immediate induction of labor versus expectant management with maternal and fetal monitoring. The study also analyzed severe maternal morbidity, maternal quality of life and costs, and neurodevelopmental and neurobehavioral outcomes at 2 years after birth. The study concluded that in women with suspected IUGR at term, there were no significant differences in adverse maternal or neonatal outcomes between induction of labor and expectant monitoring.[36-40]

A recent prospective multicenter observational trial found that abnormal umbilical artery and an estimated fetal weight <3rd percentile were associated with adverse perinatal outcome.[41]

Timing of delivery for very premature growth-restricted fetuses

It is not currently possible to identify optimal timing of delivery for very premature growth-restricted fetuses. In the United States, most physicians make the decision to deliver based on abnormal antenatal testing, an abnormal BPP, or a Category II or III NST. In terms of survival rate, the growth-restricted fetus delivered at >25 and <30 weeks is the most problematic. In our experience, growth-restricted fetuses delivered at <25 weeks' gestation do not survive; at the other extreme, all growth-restricted fetuses survive when delivered at >30 weeks' gestation.[42]

There is an absence of robust data to rely on to determine the optimal timing of delivery for very premature growth-restricted fetuses. It is our insti-

tution's practice to manage our growth-restricted fetuses based on gestational stage. We deliver very early IUGR fetuses in the presence of either a Category III NST or an abnormal BPP (4/8 confirmed at 2 hours apart in presence of Category II NST, or in the presence of a BPP of 2/8 independent of the NST).

Doppler ultrasound as an indication for delivery

As noted above, fetuses with Stage I or higher IUGR involving abnormal Doppler studies should be monitored closely. Antenatal testing is recommended and frequency ranges from twice weekly to multiple times daily, depending on level of severity. Delivery solely on the basis of abnormal Doppler studies has not been proven beneficial and, in most cases, fetuses with abnormal Doppler studies do well in the setting of reassuring antenatal testing. If antenatal testing is Category III, then immediate delivery is warranted.

Delivery mode for IUGR fetuses

Data support cesarean delivery when there is absent or reversed flow of the umbilical artery because these fetuses rarely tolerate attempts at vaginal delivery. Care must be individualized, however, because a fetus ≥34 weeks with an abnormal umbilical artery S/D ratio but a normal BPP is not likely to tolerate labor.

Summary

IUGR secondary to placental insufficiency remains a major cause of perinatal morbidity and mortality in the United States. No single test is superior to others for determining timing of delivery of the growth-restricted fetus.

At our institution, we base the decision on category of the NST or on the abnormal BPP. We monitor severe IUGR fetuses (reversed flow of the umbilical artery and/or reversed flow of the ductus venosus) with 3 NST/day (every 8 hours) and 1 BPP/day. We also administer antenatal corticosteroids in these cases. In some cases, the fetal heart rate is continuously monitored. We believe that by gaining a few days or a week between 25 and 30 weeks' gestation, we can make a difference in the future of the IUGR fetus.[33] COG

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ACA's most vexing questions

Physicians should brace for patients' confusion about the rules, reimbursements, and protocols regarding insurance

BY **LISA ZAMOSKY**

From the pages of
Medical Economics
SMARTER BUSINESS. BETTER PATIENT CARE.

October 1 marked the start of open enrollment under the Affordable Care Act (ACA), and physicians need to prepare for the possibility of increasing call volume, patient questions, and greater administrative complexities.

Yet just as the public struggles to understand the new health insurance marketplaces that are a central feature of the law, so too do physicians.

A recent survey conducted by Deloitte Center for Health Solutions found that most primary care physicians are either pessimistic about the law or don't know enough to make a determination. Nearly 32% believe it is a step in the wrong direction. And more than half of the physician respondents don't believe the insurance exchanges will even be ready.

The staffing firm LocumTenens.com found that 57% say they are not at all familiar with the impact health plans purchased through the marketplaces will have on their business. About 35% of physicians say they don't plan to make any changes to their practices in response to the law.

TAKE-HOME MESSAGES

- An estimated 7 million to 8.5 million Americans will access the marketplaces in 2014 to obtain a health plan.
- Physicians must also decide whether to participate in the networks of the new health plans being sold through the state-based marketplaces.

But taking the time to understand the health plans newly available to consumers and how patients can tap into benefits under the law is well worth physicians' time, experts say.

"There have been a lot of benefits to the plan," says David Cutler, MD, chair of the Board of Regents of the American College of Physicians. "Screening, for instance, is much more prominent, much more accepted now, not only by Medicare, but by the commercial payers. So it's much easier for me now to screen patients, and to provide vaccinations, which historically were never covered, or weakly covered," Cutler says.

And then there's the potential to gain income on previously uncompensated care. Reid Blackwelder, MD, president-elect of the American Academy of Family Physicians (AAFP), says that among the nearly 110,000 AAFP members, on average, physicians provide 8 visits a week for people without insurance. "So ideally, that number should drop pretty dramatically. I may have patients who are getting care that haven't before. I'm going to see patients now that have insurance coverage, which means it should help my payment structure."

Public's knowledge of the law is weak

The LocumTenens.com survey also found that 90% of doctors believe that the public has not been adequately educated about how marketplace health plans will function under the ACA. According to a Kaiser Family Foundation poll taken earlier this summer, fewer than 1 in 4 Americans knew that the marketplaces existed; nearly 1 in 5 were unaware that the ACA was the law of the land.

In addition, Kaiser found that 43% of those surveyed had an unfavorable view of the law, compared with just 35% who viewed the law in a positive light. This is despite the fact that many consumers have much to gain from many provisions of the ACA. For example, nearly half of those under the age of 65 surveyed believe that they or someone they live with has a pre-existing condition, and 1 in 4 have either been denied insurance or had their premium increased as a result of an illness—2 practices the law prohibits starting in 2014.

Often, however, details of what's contained in the law have been lost in the political battle. "People get ideas in their head that are influenced by something other than logic or reason, and I think it's the nature of 24/7 news, and a lot of people who legitimately don't like the Affordable Care Act," Cutler says.

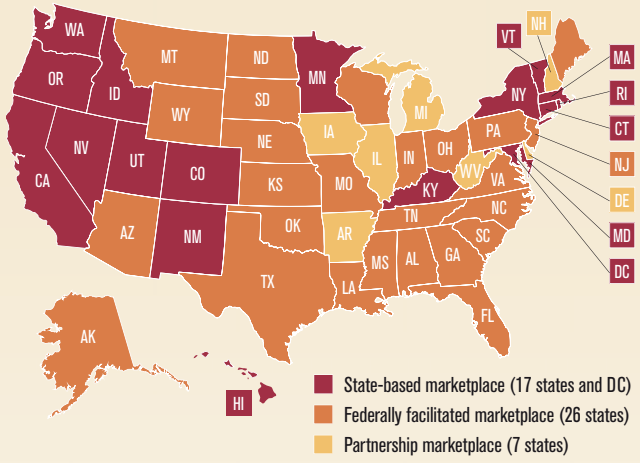
Once they understand what's in the law and how they and their families can benefit, he says, perceptions often change.

"My patients very much appreciate, and have for several years now, the fact that their children can be on their plan up to the age of 26. They can't be dropped because (their care) costs too much. Pre-existing conditions are starting to go away as a reason to be turned down for insurance," Cutler says.

An estimated 7 million to 8.5 million Americans will access the marketplaces in 2014 to obtain a health plan. Most people will have very little or no experience with insurance and will need guidance, experts say, and many will turn to doctors for information. A recent nationwide survey conducted by Healthpocket.com, which compares and ranks health plans, found that 14% of respondents who intended to seek advice on health plans preferred to get it from their doctor or pharmacist.

According to Blackwelder, when a physician sees a sick patient without insurance it is his or her role—

FIGURE 1 Health insurance exchanges



Source: U.S. Department of Health and Human Services

Resource for states operating in the Federal Exchange or Partnership Marketplace

Web site: *Healthcare.gov*

Resources for state/district insurance exchanges

California: Covered California
Web site: *coveredca.com*

Colorado: Connect for Health Colorado
Web site: *connectforhealthco.com*

Connecticut: Access Health CT
Web site: *accesshealthct.com*

Washington, D.C.: DC Health Link
Web site: *healthreform.dc.gov*

Hawaii: Hawaii Health Connector
Web site: *hawaiihealthconnector.com*

Idaho: Your Health Idaho
Web site: *yourhealthidaho.org*

Kentucky: Kentucky Health Benefit Exchange
Web site: *kynect.ky.gov*

Maryland: Maryland Health Connection
Web site: *marylandhealthconnection.gov*

Massachusetts: Health Connector
Web site: *mahealthconnector.org*

Minnesota: MN Sure
Web site: *mn.gov/hix*

Nevada: Nevada Health Link
website: *nevadahealthlink.com*

New Mexico: New Mexico Health Insurance Exchange
Web site: *nmhix.com*

New York: New York State of Health
Web site: *healthbenefitexchange.ny.gov*

Oregon: Cover Oregon
Web site: *coveroregon.com*

Rhode Island: HealthSourceRI
Web site: *healthsourceri.com*

Utah: Avenue H (for small businesses; healthcare.gov for individuals)
Web site: *avenueh.com*

Vermont: Vermont Health Connect
Web site: *healthconnect.vermont.gov*

Washington: Washington Health Plan
Web site: *wahealthplanfinder.org*

WHAT'S COVERED?

All private health insurance plans in ACA health insurance exchanges will offer the same set of essential health benefits, including:

- Ambulatory patient services
- Emergency services
- Hospitalization
- Maternity and newborn care
- Mental health and substance use disorder services, including behavioral health treatment (including counseling and psychotherapy)
- Prescription drugs
- Rehabilitative and habilitative services and devices (services and devices to help people with injuries, disabilities, or chronic conditions gain or recover mental and physical skills)
- Laboratory services
- Preventive and wellness services and chronic disease management
- Pediatric services

Source: U.S. Department of Health and Human Services

or that of someone on the team—to direct the patient toward state resources. "I think we must do that. And we have to be able to do that regardless of our personal opinion, because it is law, and it is designed to increase the healthcare coverage of Americans," he says. "How people move forward after October 1 really depends a lot on making sure they understand their responsibilities," he says.

Still, physicians often report being overwhelmed by the growing demands of running a practice. Taking the time to understand the health reform law and help patients select the right health plan is for many another burdensome task they simply don't have time for. But there are fairly simple systems that medical practices can put in place to reduce the burden, say both Cutler and Blackwelder.

Use a team-based approach

Implementing a team-based approach to patient care can go a long way toward reducing the burden of new pressures brought on by the law.

"It would help to have someone in your practice specifically for this role," Blackwelder says. "It would really make sense to have somebody who … knows the resources. When a patient came in, if someone was identified as a new enrollee or potentially someone who could benefit from the exchange, then there would be an opportunity for someone in the front office to have that conversation."

Starting a dialogue with patients, rather than jumping in with facts about the ACA, can make it easier to provide useful information. "You can't just give facts to overcome fear," Blackwelder says. He suggests asking open-ended questions, directly identifying patients' emotional state and giving them a chance to express their position before explaining details of the law and how it might affect them.

Don't recreate the wheel. So much of this, in general, is "how you work smarter and not harder," Blackwelder says. Many resources are available to explain details of ACA provisions for both physicians and consumers.

The government-created health reform web site Healthcare.gov explains the law and provides tools and information about each of the state marketplaces including Web sites and phone numbers. (See the list of ACA resources on page 39.)

The American College of Obstetricians and Gynecologists (ACOG) offers a helpful resource page called "Health Care Reform" (acog.org/About_ACOG/ACOG_Departments/Health_Care_Reform) with sections "The Law," "Your Practice," and "Your Patients."

Creating a handout listing resources where your patients can go for personalized assistance to learn about their health insurance options provides an important service.

Important contracting considerations

Physicians also have numerous administrative issues to deal with under the law. One of the more immediate concerns is whether or not to participate in the networks of the new health plans being sold through the state-based marketplaces. And despite the late date, many of the networks have not been solidified.

"There is a lot of variability across the states in terms of where practices are with their contracting with payers and making decisions about how to or whether or not to participate with these exchange products," says Allison Brennan, senior advocacy advisor with the Medical Group Management Association.

Among the questions she hears from physicians, many concern payment rates, the size of the patient population insurers expect to serve, and which insurers are offering products through the marketplace.

Divigel® is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

What a sigh of relief feels like

- Divigel® 1 mg/day eliminated nearly 9 out of 10 daily hot flashes at week 12[1]
- Reductions in median daily frequency of moderate to severe vasomotor symptoms, which include night sweats, by dose at week 12: 87% (1 mg/day), 79% (0.5 mg/day), 71% (0.25 mg/day), and 48% (placebo)[1,2]*

*In a study of 488 postmenopausal women (34-89 years of age) who received 1 mg (n=124), 0.5 mg (n=119), or 0.25 mg (n=121) of Divigel®, or placebo gel (n=124) daily.

References: 1. Divigel® [package insert]. Minneapolis, MN: Upsher-Smith Laboratories, Inc; 2012. **2.** Data on file. Upsher-Smith Laboratories, Inc.

Divigel® (estradiol gel) 0.1%

0.25 mg 0.5 mg 1 mg

www.divigel.com

Important Safety Information for Healthcare Providers

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

See Full Prescribing Information for complete Boxed Warning

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

Divigel® should not be used in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to Divigel®; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; or known or suspected pregnancy.

Estrogens increase the risk of gallbladder disease.

Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs.

Monitor thyroid function in women on thyroid replacement therapy.

The most common adverse reactions (incidence ≥ 5 percent) are breast tenderness, metrorrhagia, vaginal mycosis, nasopharyngitis, and upper respiratory tract infection.

Patients should be started with the lowest effective dose and the dose should be evaluated periodically.

Alcohol-based gels are flammable. Patients should avoid fire, flame or smoking until the gel has dried.

Please see Full Prescribing Information, including Boxed Warning and Patient Counseling Information. For more information, call 1-888-650-3789 or visit www.divigel.com.

You are encouraged to report negative side effects to Upsher-Smith Laboratories, Inc. at 1-855-899-9180 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

Please see accompanying Brief Summary on adjacent page.

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Brief Summary of Prescribing Information

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.

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

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

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

INDICATIONS AND USAGE

Divigel is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

CONTRAINDICATIONS

Divigel® should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to Divigel
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

WARNING AND PRECAUTIONS

Cardiovascular Disorders- An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately. *Stroke* - In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) .The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. *Coronary Heart Disease*- In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2]. Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years)[1]. In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[1]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism*- In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms**- *Endometrial Cancer*- An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer*- The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[2]. The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups[6]. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial date on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer* - The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 [95 percent CI, 0.77-3.24]. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. **Probable Dementia-** In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8]. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 womenyears[8]. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Gallbladder Disease-** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia -**Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities-** Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy-** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure-** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia-** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice-** Estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism-** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention-** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia-** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis-** A few cases of malignant transformation of residual endometrial implants have been reported in women treated post hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered. **Hereditary Angioedema** Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. **Exacerbation of Other Conditions** Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. **Photosensitivity/Photoallergy** The effects of direct sun exposure to Divigel application sites have not been evaluated in clinical trials. **Application of Sunscreen and Topical Solutions** Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of sunscreens and other topical lotions on the systemic exposure of Divigel has not been evaluated in clinical trials. **Flammability of Alcohol-Based Gels - Alcohol based gels are flammable.** Avoid fire, flame, or smoking until the gel has dried. Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried. **Potential for Estradiol Transfer and Effects of Washing** There is a potential for drug transfer from one individual to the other following physical contact of Divigel application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects; however, the degree of transferability in this study was inconclusive. Patients are advised to avoid skin contact with other subjects until the gel is completely dried. The site of application should be covered (clothed) after drying. Washing the application site with soap and water 1 hour after application resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol. Therefore, patients should refrain from washing the application site for at least one hour after application. **Laboratory Tests-** Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms. **Drug - Laboratory Test Interactions -** Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning]*.
- Malignant Neoplasms *[see Boxed Warning]*.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for Divigel. **Metabolic Interactions -** *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy Divigel should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy. **Nursing Mothers-** Divigel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when Divigel is administered to a nursing woman. **Pediatric Use-** Divigel is not indicated in children. Clinical studies have not been conducted in the pediatric population. **Geriatric Use-** There have not been sufficient numbers of geriatric women involved in studies utilizing Divigel to determine whether those over 65 years of age differ from younger subjects in their response to Divigel. *The Women's Health Initiative Studies* In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

The Women's Health Initiative Memory Study In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Renal Impairment-** The effect of renal impairment on the pharmacokinetics of Divigel has not been studied. **Hepatic Impairment-** The effect of hepatic impairment on the pharmacokinetics of Divigel has not been studied.

OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Divigel therapy with institution of appropriate symptomatic care.

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In many markets, newer payers with whom many physicians may not have experience have entered the market. "One of the things that we've been hearing is just the uncertainty and the variation across states in terms of where practices and payers are in that contract negotiating process," Brennan says.

As practices consider the contracts before them, Brennan advises watching for several items when deciding whether to participate in marketplace plans:

1. Look at payer mix. "We recommend our members evaluate their practice's payer mix and determine how much capacity they would have to accept new patients," Brennan says.

2. Reach out to payers you want to work with. "If the payers have already been identified in your exchange, and you want to participate, you can reach out to them and try to initiate that discussion and start to have those contract negotiations," Brennan says.

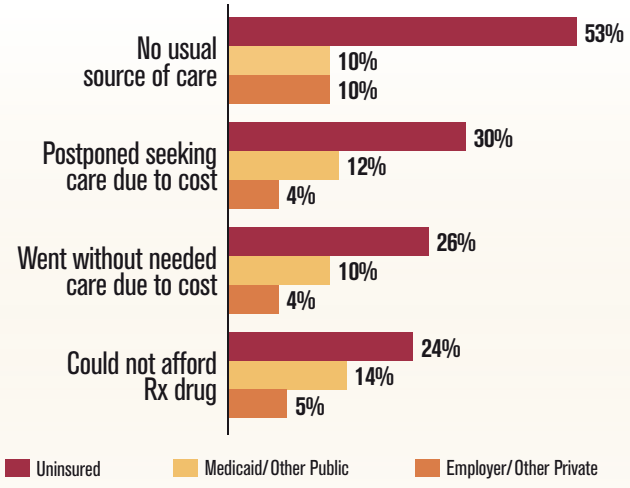
Watch for communication from insurers. According to Brennan, some insurers are requiring practices with whom they have already contracted to actively opt out of contracting for the exchange plans if they wish not to participate.

"So, rather than the plan calling them up and saying, 'Hey, do you want to contract for this exchange product,' what they're doing is sending them a letter that says, 'Unless you respond to this within 7 days, we'll assume that you'll be participating in this new plan,' " he says.

3. Pay close attention to contract details. One major concern for physician practices is contract language that allows for a 90-day grace period for a patient who has an exchange plan and stops paying his or her premium. During the first 30 days of that period, the insurer is required to continue to pay claims. But in the last 60 days, payment can be withheld. If the patient fails to pay all of his or her premiums, they'll lose the coverage at the end of the 90 days, and physicians will be required to collect any withheld payments directly from the patient.

"That puts an unfair burden on providers, especially if they don't know that a patient is in this grace period," Brennan says. "So we would like to see Congress or [the Centers for Medicare and Medicaid Services] change this grace period provision to protect providers, and at the very least, they should make some specific changes requiring insurers to provide up-to-date information when a patient enters the grace period," Brennan says.

FIGURE 2 Barriers to healthcare among non-elderly adults by insurance status, 2011

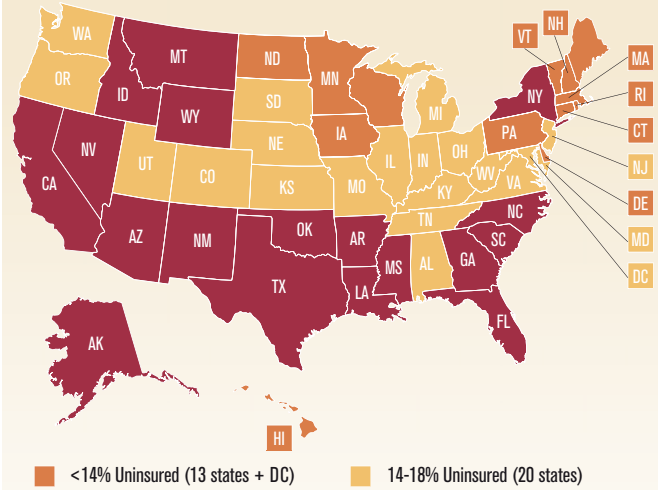


Source: Kaiser Commission on Medicaid and the Uninsured

As a matter of protection, she says, practices need to conduct eligibility verification requests at every visit.

And it's worth requesting that some of that liability shift back to the insurer or requiring contract language that says the insurer will notify the practice when the patient has entered the grace period.

FIGURE 3 Uninsured rates among the nonelderly by state, 2010-2011



Source: KCMU/Urban Institute analysis of 2012 ASEC Supplement to the CPS.

FIGURE 4 2014 standard benefits for individuals in California State Health Insurance Exchange

	Bronze	Silver	Gold	Platinum
Deductible	$5,000	$2,000	No deductible	No deductible
Preventive copay	No cost (1 yearly)	No cost (1 yearly)	No cost (1 yearly)	No cost(1 yearly)
Primary care visit copay	$60 (3 a year)	$45	$30	$20
Specialty care visit copay	$70	$65	$50	$40
Urgent care visit copay	$120	$90	$60	$40
Lab testing copay	30%	$45	$30	$20
Generic medication copay	$19	$19	$19	$5
X-ray copay	30%	$65	$50	$40
Emergency room copay	$300	$250	$250	$150
Hospital care, outpatient surgery	30% of plan's negotiated rate	20% of plan's negotiated rate	HMO*	HMO**
Imaging (MRI, CT, PET scans)	30%	$250	$250	$150
Brand medications (may be subject to annual drug deductible)	$50-$75 after deductible	meet $250 deductible	no deductible	no deductible
Preferred brand copay after drug deductible (if any)	$50	$50	$50	$15
Maximum out-of-pocket for individual	$6,350	$6,350	$6,350	$4,000
Maximum out-of-pocket for family	$12,700	$12,700	$12,700	$8,000

*Outpatient surgery: $600; hospital, $600/day up to 5 days
** Outpatient surgery: $250; hospital, $250/day up to 5 days

Source: Covered California

4. Evaluate and revamp payment and collections policies and procedures. This is especially important if your practice treats many patients with high-deductible health plans, which will be common among those purchasing coverage through the exchanges.

An alarming study from Jackson Hewitt concludes that more than 1 in 4 uninsured Americans (approximately 8.5 million people) eligible for the new ACA premium assistance tax credits do not have a checking account, the vehicle through which insurance companies plan to require customers to pay healthcare premiums.

5. Know your state. While the health reform law seeks to create uniformity in health plan offerings, there are still wide variations among the states. Brennan suggests doctors stay abreast of what's happening in their area. "They have to make sure they're really tracking how this is evolving in their state, and in their local market," she says.

A new world awaits

The true impact of the ACA and whether the marketplaces will operate as promised, whether enough consumers will buy insurance policies, and how heavily affected ob/gyn practices will be all remain to be seen.

Will we end up with a healthcare system that works better for consumers and physicians alike in the long run? "I'm an optimist," Blackwelder says. "I'm not going to say I'm sure it will work. Then again, the flip side of that is, it would be hard pressed to do worse than some of the systems we've already suffered through." COG

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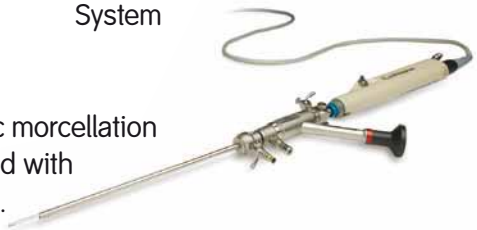

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BY **JON I. EINARSSON, MD, PHD, MPH**

Technology and the ob/gyn

It's an interesting time to be a gynecologic surgeon. As technologies evolve and refine, we and our patients will benefit.

We are completely surrounded by technology in our personal and professional lives. While technology may be helpful, it can also complicate tasks that used to be simple. As an example, consider the evolution of the surgical removal of a uterus. The first such procedure was performed in a living room without anesthesia and with very simple instrumentation. While the patient survived, the modern performance of a hysterectomy has become much safer, in large part thanks to the evolution of technology. This evolution has given surgeons myriad complex tools and several options for modes of access, but it has also made it challenging for gynecologists to remain proficient in the safe use of all instruments and surgical methods.

> In this special supplement **we explore important technology principles that are relevant** to day-to-day clinical practice.

In this special supplement we explore important technology principles that are relevant to day-to-day clinical practice.

Dr. Peter Lim outlines some tips and tricks for the successful implementation of a robotic surgery program. Since its US Food and Drug Administration approval for gynecologic applications in 2005, robot-assisted laparoscopy has enjoyed a rapid rise in utilization, to the point where robotic hysterectomy has replaced robotic prostatectomy as the most common robotically assisted laparoscopic procedure in the United States.

While the use of robotics may enable certain surgical tasks, the robotic system adds a layer of complexity due to unique instrumentation, a large footprint, and a physical distance between surgeon and patient. It is important that surgeons are aware of these issues and take steps to avoid any undue effects that may arise as a result.

Dr. Lim's article on robotic surgery discusses important principles such as port placement, instrument choices, and robotic docking, all of which are critical to safe robotic surgery.

Dr. Craig Sobolewski discusses the use of electrosurgery. While all gynecologic surgeons utilize electrosurgery regularly, many do not understand the basic principles behind this technology. This is unfortunate because improper

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use of electrosurgery is one of the leading causes of patient injury at the time of surgery.

The segment on electrosurgery will help the reader to better understand and implement the safe utilization of electrical energy in his or her surgical practice.

In Point/Counterpoint, Dr. Rosanne Kho debates Drs. Ted Lee and Cara King on the subject of whether surgeons should choose the laparoscopic or vaginal approach when performing a minimally invasive hysterectomy. While the American College of Obstetricians and Gynecologists currently recommends the vaginal approach as the primary mode of access, the implementation of vaginal hysterectomy in clinical practice has been stagnant for decades. This is unfortunate because this approach is the most cost-effective, and several authors have published extensively on its safety even in situations with challenging pathologies.

Dr. Kho describes current efforts and strategies to change this trend, as well as the importance of several technical approaches to increase surgeon success and decrease complications.

On the other hand, Drs. Lee and King discuss how, considering the complexity of gynecologic surgery and the wealth of surgical options available, it is impossible for the average practitioner to remain competent in all surgical approaches. They also argue that the laparoscopic approach is the more logical choice in light of recent reports of lower postoperative morbidity as compared with vaginal hysterectomy.

Furthermore, laparoscopic hysterectomy may be more universally applicable than vaginal hysterectomy in a variety of clinical scenarios. Readers will undoubtedly come to different conclusions based on their own surgical experience, but this debate provides food for thought for all gynecologic surgeons.

Finally, the *Contemporary OB/GYN* Tech Tools columnists, Drs. Brian Levine and Dan Goldschlag, discuss the latest technologies that cross the boundaries between personal and professional applications. New devices and apps that open new avenues to connectivity, syncing, and 3-D mapping will one day—perhaps much sooner than we expect—affect the ways we all practice.

It is an interesting time to be a gynecologic surgeon. While the variety of complex technology may seem daunting at first, it is exciting to witness the rapid evolution and refinement of our surgical field.

It will be interesting to look back 10 years from now. I predict that the surgical landscape will have changed dramatically by then. Regardless, it seems inevitable that technological advances will continue to enable surgeons to perform complicated gynecologic procedures safely and in a minimally invasive fashion, which will ultimately greatly benefit our patients. COG

DR EINARSSON, Deputy Editor, is Associate Professor of Obstetrics and Gynecology, Harvard Medical School, Boston, Massachusetts, and Director, Division of Minimally Invasive Gynecologic Surgery, Brigham and Women's Hospital, Boston, Massachusetts.

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Robotics in gynecologic surgery

The surgeon's guide to positioning, port placement, safety, efficiency, and payment.

BY **PETER C. LIM, MD**

DR. LIM is Medical Director of gynecologic oncology and robotic surgery at the Center of Hope, Reno, Nevada, and Medical Director of the Minimally Invasive Surgical Institute, Renown Regional Medical Center, Reno, Nevada.
He has no conflict of interest to report with respect to the content of this article.

The introduction of da Vinci robotic surgery (DVRS) to the field of gynecologic surgery has made minimally invasive procedures a possibility for a growing number of patients for whom open surgery was once the only option. Laparoscopy historically has been proven to have advantages over open surgery including shorter hospitalization, faster recovery, less blood loss, better cosmesis, and fewer complications.

Applications for laparoscopic vaginal procedures, however, can be limited by complex pathology. Traditional laparoscopy also relies on hand movements that are counterintuitive and instruments with a limited range of motion that often require ergonomically challenging positions. Both vaginal and traditional laparoscopy can also be challenging because of limited operative field visualization and the requirement for a skilled surgical assistant. Such challenges can lead to fatigue and frustration for a surgeon. Consequently, the rate of abdominal hysterectomy remains over 60% while the rate of vaginal hysterectomy remains stagnant at 22% and laparoscopic hysterectomy at 14% despite the existence of these minimally invasive surgical approaches for over 20 years.[1,2]

TAKE-HOME MESSAGES

- The learning curve is different for each part of a robotic surgical procedure.
- The debate continues as to whether utilization of a robotic surgery platform may increase the overall economic burden on the healthcare system.
- Surgeons should be supervised or assisted by experienced colleagues until satisfactory competency has been achieved.

Robotic surgery became a reality when the US Food and Drug Administration (FDA) approved AESOP (Automated Endoscopic System for Optimal Positioning), a single robotic arm that was controlled by voice command. In 1999, 2 robotic arms were added to create the ZEUS robotic surgical system, which also introduced the concept of a surgeon operating at a distance from the patient, now known as

telesurgery. This technology was further advanced by Intuitive Surgical, which added a console that allows the surgeon to view the operative field through a screen and direct movement of instruments through robotic arms via finger graspers and foot pedals. It has a high-definition camera vision system that provides a 3-dimensional image of the operative field controlled via foot pedals and arm movements. In addition EndoWrist instruments allow 7 degrees of freedom, mimicking natural hand and wrist motions intuitively, much like open surgery.

In April 2005, the FDA approved robotic technology for gynecologic surgery. Since then the adoption of robotic surgery has been rapid. Several academic teaching hospitals have reported a dramatic decrease in both open hysterectomies and traditional laparoscopic surgeries while the rate of robotic surgery increased dramatically.[3,4]

Safe use of robotic surgery

Surgeons who want to adopt robotic surgery must be properly trained, familiar with the tools, and committed to safe use of the technology. Currently there is no formal clinical pathway recommended by any of the gynecologic societies or the American College of Obstetricians and Gynecologists (ACOG), with the exception that ACOG recommends supervision or assistance by an experienced colleague until satisfactory competency has been achieved.[5]

One researcher has proposed a detailed clinical pathway based on the results of informal surveys from experienced robotic surgeons, which involves didactic study, dry laboratory on the robotic platform or simulator, case observation, and a live animal laboratory model, followed by proctored cases.

A minimum of 3 simple cases proctored by an experienced robotic surgeon was proposed for the first 3 cases, and at least 12 to 15 simple robotic surgical cases should be performed before an advanced case is attempted.[6] A detailed clinical pathway should be adopted to safely employ this technology and minimize complications.

Obtaining robotic surgery efficiency

Achieving robotic surgical efficiency involves team effort, preparation, and commitment. A coordinated team effort is imperative to achieving robotic surgical efficiency. The team consists of a robotic coordinator, surgeon, first assist, a circulator, surgical tech, and an anesthesiologist. The robotic coordinator troubleshoots for potential system failure and

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS INC.

provides system maintenance. Each team member is assigned specific tasks. For example, the bedside assistant manages the respective robotic arms while a second assistant manages the uterine manipulator. There should be clear and constant communication between these bedside assistants and the surgeon to minimize wasted movements. In addition, the bedside assistants should be knowledgeable in managing robotic arm collisions.

Commitment to training is essential for a surgeon who wants to become proficient in robotic surgery. How many robotic surgical cases are required to achieve efficiency with the technology remains unclear. A retrospective cohort study, however, reported that between 25 and 50 cases are required to achieve proficiency in the early learning curve for both benign and malignant hysterectomies.[7-9] Furthermore, it is important to recognize that the learning curve is different for each part of a robotic surgical procedure—port placement, docking, hysterectomy, cuff closure, and lymph node dissection.[7,10]

Early adopters of robotic surgery should commit to performing multiple consecutive robotic surgical cases to develop and maintain skills such as multiple clutching, tracking, and wristing instruments to become efficient. Use of a computerized robotic simulator, similar to the inflight-simulators used for

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TABLE Surgical steps for robotic hysterectomy and recommended instrument options

	Surgical steps	EndoWrist instrument options	Ancillary supplies and scope
1	**Right-sided hysterectomy:** Incise broad ligament, identify right ureter and internal iliac artery and vein. Transect round ligament and infundibulo-ovarian ligament (for removal of adnexa) or utero-ovarian ligament (preservation of adnexa). **Develop vesicouterine reflection.** **Develop bladder flap and indentify ureter.** Coagulate and transect right uterine vessels, right cardinal ligament. **Left-sided hysterectomy:** Incise broad ligament, identify left ureter and internal iliac artery and vein. Transect round ligament and infundibulo-ovarian ligament (for removal of adnexa) or utero-ovarian ligament (preservation of adnexa).	**Monopolar instruments:** Hot shears (monopolar curved scissors), spatula, or harmonic scalpel. Place in robotic arm port 1 in the surgeon's dominant hand. **Bipolar instruments:** Fenestrated bipolar forceps or Pk dissecting forceps or Maryland bipolar forceps placed in robotic port 2, in the nondominant hand. **3rd arm option:** Prograsp forceps to assist in countertraction.	Uterine manipulator is placed in the uterus to provide traction and countertraction. 0-degree robotic scope is placed in the camera port. 5-mm atraumatic grasper (45 cm long) is placed via the assistant port to assist in retraction. Raytek sponge may be placed via the assistant port to clear the operative field (we discourage the use of suction irrigator to minimize splash-back of the camera and also loss of pneumoperitoneum).
2	**Colpotomy:** Identify the colpotomy ring, incise circumferentially along it, and transect uterosacral ligaments. The specimen is then removed vaginally and pneumoperitoneum is maintained via placement of wet lap sponges in the vaginal canal.		A wet lap sponge is placed in the vaginal canal to maintain pneumoperitoneum.
3	**Vaginal cuff closure:** Using running or interrupted sutures, incorporate vaginal mucosa and peritoneum with each suture placement. Incorporate uterosacral ligaments laterally. Ensure hemostasis.	EndoWrist Mega Suture Cut needle driver is placed via port 1 and EndoWrist large needle driver is placed via port 2 for cuff closure.	0-Vicryl, Quill PDS, V-Loc sutures are used to close the cuff. A 5-mm atraumatic grasper is placed via assistant port to deliver sutures for cuff closure.

pilot training in aviation, is helpful for maintenance of robotic surgery skills and proficiency.[6]

Finally, clear, consistent steps for each specific surgical procedure should be adopted so that team members can become familiar with each procedure with repetition. One such proposal for procedural steps for a robotic hysterectomy is outlined in the Table (see also Video 1).

Patient positioning and robotic port placement

Patient positioning

For robotic surgery, a patient is placed in a low lithotomy position with legs padded in yellow fin stirrups (Allen Medical Systems) in a Trendelenburg position. Arms are tucked and padded to minimize any nerve injury. Shoulder braces can be used to minimize the known risk that a patient in steep Trendelenburg will slip from the table. The braces should be well padded to minimize brachial plexus injury. It is important to note that a steep Trendelenburg position for more than 3 hours may predispose a patient to potential brachial plexus injury, corneal abrasions, laryngeal edema, cerebral edema, and posterior ischemic optic neuropathy.[10] The etiology of these potential intraoperative complications is unclear. It is believed, however, that prolonged steep Trendelenburg position may be a contributing factor, particularly in patients with a body mass index greater than 30.

Port placement

Proper port placement is imperative not only to minimize potential complications but also because it will dictate the success of the procedure. Robotic surgical platforms have the option of using a 2-arm system or a 3-arm system. A 2-arm system can be used to minimize cost; however, when employing the 2-arm system a surgical assistant is required to assist in

the operation. We prefer to utilize all 3 robotic arms with the 3rd arm providing static counter traction in place of the assistant surgeon. The steps for port placements are outlined in the Figure.

Step 1: Planning and adjusting for body surface. Adjustment of the port placements according to the patient's abdominal wall body surface area is imperative. Typically, the camera port is placed first at the midline at the level of the umbilicus. The robotic ports are then placed 8 to 10 cm lateral to the camera port. In a thin patient, however, it is important to place the camera port 2 cm lateral to the umbilicus, contralateral to ports 1 and 3. This port placement adjustment is important for port 3 to avoid the flank region, which would limit arm function.

VIDEO

Video 1: Five steps to robotic hysterectomy
www.contemporaryobgyn.net/robotic_hysterectomy_5_steps

Our preference is to place ports 1 and 3 in the right upper quadrant mainly because of the surgeon's right-handed dominance. Port 2 is placed in the left upper quadrant while the camera port is placed between port 1 and port 2 (Figure). If the surgeon is left-hand dominant, then ports 1 and 3 can be placed in the left upper quadrant while port 2 is placed in the right upper quadrant.

An incision is made where the camera port will be placed at the midline and pneumoperitoneum is established followed by demarcation of port placements. A 12-mm trocar is then placed at the camera port site and initial exploratory laparoscopy is performed to evaluate the peritoneal cavity for adhesions. We prefer to use a separate 5-mm laparoscope to perform this function. The 5-mm laparoscope facilitates maneuverability in the event that adhesiolysis is required.

Step 2: Placement of assistant port in left lower quadrant. The assistant port is placed after the camera port. The assistant port is placed inferiorly in the left lower quadrant 2 cm ipsilateral to port 2 at the level of the anterior superior iliac spine. Placement of the assistant port in the left lower quadrant has several advantages: it allows the surgeon to visualize the upper abdomen during placement of instruments through the robotic ports thereby minimizing internal organ injury; it allows the surgeon to track and assist in removal of suture with needles to prevent a lost needle; and it minimizes "chopsticking" with the robotic arms at the time of pelvic dissection. In the event that robotic ports are displaced when pneumoperitoneum is lost during surgery, utilization of a conventional 5-mm laparoscope via assistant port allows diagnosis of any robotic port problems without re-docking the robotic camera.

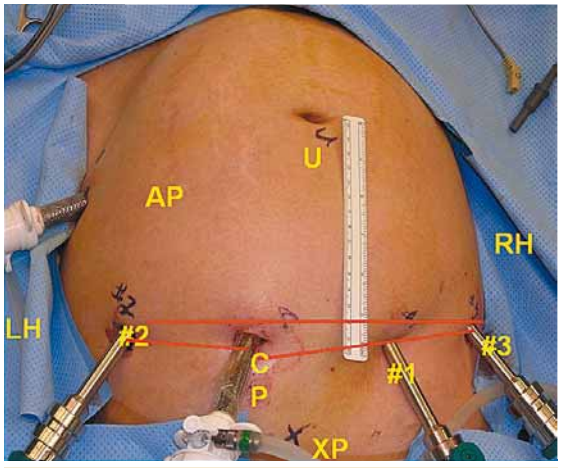
Step 3: Placement of robotic ports. Employing a separate 5-mm conventional laparoscope via the assistant port allows for safe placement of robotic ports and instruments under direct laparoscopic visualization. The robotic ports are generally placed such that they are in a straight line to minimize arms clashing. The ports are generally placed at the level of the umbilicus. They should, however, be adjusted cephalad, to accommodate complex surgical cases such as large fibroids, obese patients, or para-aortic lymph node dissection (see Video 2).

Once the ports are appropriately placed, the robot is docked to allow attachment of robotic arms to the robotic ports. Depending on the intended surgical procedures, the robot is docked either at the patient's hip (also called side docking), shoulder, or perineum. For a majority of pelvic surgical procedures, side docking is recommended as it allows for vaginal access. If side docking is preferred, the robot should be docked ipsilateral to ports 1 and 3.

Instrumentation

Proper instrumentation is critical to perform robotic surgery successfully. A bipolar grasper or PK dissector is placed in port 2 in the contralateral nondominant hand to grasp, coagulate, and seal vessels. A unipolar spatula, monopolar hot shears (scissors), or harmonic scalpel is typically placed in port 1 in the dominant hand to facilitate dissection. We prefer to use the unipolar spatula in the dominant hand; however, the disadvantage is that it does not allow for spreading and separating the tissue to identify tissue planes. The hot shears or harmonic scalpel is a better instrument if this surgical technique is desired. The advantage of the harmonic scalpel is that the blunted blades allow for tissue grasping, which cannot be accomplished with hot shears. Prograsp forceps are typically placed via port 3 to provide static counter traction to facilitate dissection.

FIGURE Steps for port placement



1. Achieve pneumoperitoneum before port marking
2. Place the patient in steep Trendelenburg
3. Adjust the port marking based on body surface area
4. **Camera port (C)**
   - Thin patient: 2 cm off to the midline umbilicus (contralateral to the third arm)
   - Obese patient: at the level of umbilicus
5. **Port #1 ideal placment:** 8-10 cm lateral to the camera port (C)
6. **Port #2 ideal placment:** 8-10 cm lateral to camera port
7. **Port #3 ideal placment:** 8-10 cm lateral in relation to port #1. Final position is 2 cm lateral to midclavicular.
   - Right upper quadrant
8. All the ports are aligned about 5 degrees
9. Place assistant port in lower quadrant (usually at the level of ASIS) contralateral to the dominant arm. Make sure this port is 2 cm lateral to port #2.

Abbreviations: AP, assistant port; ASIS, anterior superior Iliac spine; CP, camera port; LH, left hand; RH, right hand; U, umbilicus; XP, xyphoid process

Surgical tips to avoid complications

Complications of robotic surgery can occur as a result of malfunction of the robotic system, instrument failures, the surgeon's inexperience, trocar injuries, and poor robotic surgical techniques. The incidence of robotic system failure during surgical procedures has been reported to be 2.4% for robotic general surgical procedures and 4.5% for robotic urologic procedures and gynecologic oncology procedures.[11-13] No mortality has been reported and the need for conversion to laparoscopic or open procedure was reported to be less than 1%.

The primary instrument failure that has been reported is insulation failure on the robotic monopolar scissors tip cover accessory (MSTCA). This insulation device prevents current leak from surfaces on the instrument other than the scissors tip. In a prospective analysis, researchers reported a nearly 40% visible insulation defect and 33% electric arcing problem defect in the first-generation MSTCA.[14] They found that electrical arcing increases with greater wrist angulation and higher power setting. The insulation failure was seen after a single use of the instrument. The study did not find this in the second generation of MSTCA. Other investigators found a similar insulation failure rate (33%), but reported that the incidence of insulation failure dramatically increases to 80% after 10 uses of the instrument.[15] Thus it is important to be cognizant of this potential complication if monopolar scissors is the preferred instrument for dissecting and coagulation.

Intraoperative complications have been well documented for robotic surgery done for benign gynecologic procedures such as adnexectomy, myomectomy, benign hysterectomy, and sacrocolpopexy, as well as malignant hysterectomy, surgical staging for endometrial cancer, radical robotic hysterectomy, and ovarian cancer debulking.[6,16-32] In retrospective studies, the reported incidence of complications for robotic surgery is 2% to 10% and the complications identified include bowel, vascular, bladder, ureteral, and nerve injuries. Incidence of complications for robotic surgery is lower than for open surgery; but outcomes were no different in a retrospective comparison of perioperative outcome for robotic versus laparoscopic hysterectomy.[33]

Another prospective, randomized, controlled study also showed no difference in complications between robotically assisted total laparoscopic hysterectomy and conventional total laparoscopic hysterectomy.[34] In all these reported cases, it was difficult to ascertain the factors that contributed to the complications. Possible factors include lack of communication between the surgeon and the bedside assistant when exchanging instruments, lack of tracking instruments, thermal injury from coupling effect, and loss of haptic feedback from excessive force of traction or counter traction with the robotic arms.

Finally, inexperience and poor judgment in case selection during the early learning curve may lead to complications. Thus proper training on the robotic

platform and appropriate uncomplicated case selection in the early learning phase is encouraged. The surgeon should have the ability to troubleshoot and be aware of potential instrument defects.

Proper robotic surgical techniques such as communicating with the bedside assistant in exchanging instruments, tracking instruments, wristing instruments to avoid energy coupling effect, and avoiding grasping excessive tissue and rapid jerky movements to minimize tissue trauma during dissection should be incorporated.

Reimbursement for robotic surgery and counseling

Currently no formal CPT codes exist for payment of robotic procedures. Based on the current Medicare landscape, the 2013 nationally unadjusted payment rates for gynecologic surgical procedures performed abdominally, vaginally, laparoscopically, and robotically range from $1957 to $5121 for hospital outpatients and $5163 to $23,609 for hospital inpatients whereas the nationally unadjusted professional/physician payment rates range from $842 to $1851. Payment variations depend on factors including whether the tumor is malignant or benign, comorbidities, and whether the surgery is open or minimally invasive.

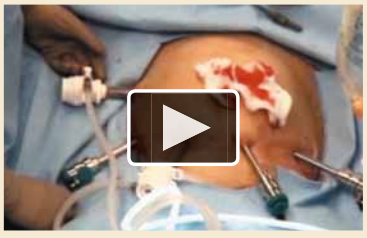
Hospital administrators have been concerned about investing in this technology because of its high cost. One economic analysis showed that direct costs and charges associated with robotic surgery were higher compared to laparoscopic surgery.[35] Actual reimbursements to the hospital, surgeon, and anesthesiologist were not significantly different, however, between these surgical approaches. Nevertheless, another recent analysis found that robotic surgery can be profitable based on operative efficiency, payer mix, and the surgical procedure performed.[36]

As more surgeons have adopted robotic surgery, the number of medical legal claims associated with it has risen. Prospective surgeons adopting robotic surgery are potentially at risk of malpractice claims because of failure to obtain informed consent and negligent credentialing. Thus it is imperative to adhere to the ACOG doctrine of informed consent when counseling patients about robotic surgery. It has also been suggested that disclosing and discussing with the patient your progress on the robotic surgery learning curve might mitigate some of the liability risks.[37]

Finally, the adoption of robotic surgery and its technology is growing. As this technology develops, it will continue to improve and influence surgical care of women. Since FDA approval of robotic surgery in 1995, there have been 3 generations of robotic platforms: the standard system, the second-generation da Vinci S system, and the most current generation da Vinci Si system. The current generation da Vinci Si system has dual console capability, which not only allows for teaching but also for the assistant surgeon to partake in the actual robotic surgery.

In addition, the da Vinci Si incorporates a simulator. Development of the simulator may allow surgeons to maintain their surgical skills. On the current Si system, robotically driven EndoWrist articulation instrumentations such as vessel sealer, suction irrigator, and GIA stapler have been developed.

VIDEO



Video 2: Port placement with side docking
www.contemporaryobgyn.net/port_placement_side_docking

Summary

Robotic surgery has completely revolutionized surgical care of women. Technologic advances such as EndoWrist instruments that mimic natural hand and wrist motions intuitively, much like open surgery, may offer an ergonomic advantage and possibly extend a surgeon's career; however, further study in this area is required for validation. The debate continues as to whether utilization of a robotic surgical platform may increase the overall economic burden on the healthcare system. The overall cost of robotic surgery is extremely difficult to ascertain. Currently no studies have objectively analyzed the true cost of robotic surgery.

Cost analysis for robotic surgery must take into account not only the initial investment in the surgical platform, the annual maintenance fee for the system, and the cost of instrumentation, but also the surgeon's proficiency, the efficiency of the operating room, and surgical outcomes. More importantly the robotic technology has allowed patients access to minimal invasive surgery who otherwise might not have been candidates for a vaginal or laparoscopic approach. COG

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Electrosurgery
the newest energy-based devices

Electrosurgical instruments aid skilled surgeons in performing safe cutting-edge procedures.

BY **CRAIG J. SOBOLEWSKI, MD**

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Use of electrosurgery is pervasive in gynecologic abdominal procedures. The technology also is common for many vaginal and operative hysteroscopic procedures. But formalized training in the safe and effective use of electrosurgery is lacking. With the exception of the use of laser energy, there is no uniform credentialing process to allow surgeons to operate with devices that apply electrical energy to tissues.

Industry-sponsored events and sales representatives provide much of the training in the use of new surgical devices. In residency, most education is limited to observing a senior resident or attending surgeon. An understanding of how electrosurgical instruments interact with tissue is essential to their safe use.

Understanding cut, coagulation, and blend waveforms

Electrosurgical devices create the effect that they have on tissues by generating heat. In fact, all modern surgical energy devices, including ultrasonic energy, laser energy, and plasma energy, work by creating heat.

With electrosurgery, the heat is generated as electrons flowing through tissue meet resistance to that flow. This is referred to as resistive heating.[1] If high temperatures are generated rapidly, the result is boiling of the intracellular water. Increased pressure inside the cell causes the cell wall to explode. As the cells are disrupted, tissue dissection occurs. Because the heat dissipates rapidly as steam or plasma, adjacent tissues receive only very minimal heat.

When using monopolar electrosurgical devices, resistive heating occurs best with the "pure cut" waveform. In the pure cut mode, energy is delivered continuously and can be described as a high current/low voltage waveform. In contrast, in "coagulation mode," the current is interrupted and, in fact, is "on" only 6% of the time. This interrupted deliv-

TAKE-HOME MESSAGES

- An understanding of the principles of how electrosurgical instruments interact with tissue is essential to their safe use.
- New surgical devices make the gynecologic surgeon's job easier, but are no subsistute for training, knowledge, and experience.

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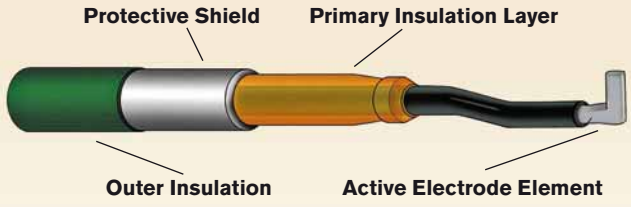
FIGURE 1 Active electrode monitoring device



A schematic of an active electrode monitoring (AEM) device. The shield is dynamically monitored for insulation failure and excessive capacitatively coupled current. When a defect is detected, the AEM monitor shuts off delivery of electrosurgical current, protecting the patient from stray energy caused by insulation failure or excessive capacitative coupling.

ery results in lower tissue temperatures, leading to protein denaturation and formation of a coagulum.

Compared with pure cut current, coagulation current is a low current/high voltage form of electrosurgical energy. With higher voltage, the heat generated has a greater potential to deeply penetrate tissue. Therefore, although coagulation current may generate lower tissue temperatures, the higher voltage can result in substantially greater and potentially unrecognized lateral thermal spread.

Understanding this fundamental difference is critically important for a gynecologic surgeon, especially because the names assigned to these waveforms imply different clinical effects. The word "cut" sounds more dangerous than the word "coagulate," but it is possible that cut current will be far safer if the goal is to minimize lateral thermal spread.

Modern electrosurgical units (ESUs) have begun to address this important issue of voltage by evolving into "adaptive" generators.[2] These ESUs are capable of determining tissue resistance that is encountered by the tip of the electrode and relaying that information back to the generator. The ESU, in turn, adjusts its internal algorithms to ensure that there are no voltage spikes and that power output remains constant. That may allow the surgeon to achieve the same clinical effect at lower wattage settings than required by generators.

As with medications, using the lowest "dose" of electricity over the shortest time may be the safest way to operate with energized devices.

Newer waveform technology

In addition to the standard "cut," "coagulate," and "blend" waveforms, one ESU manufacturer has used adaptive technology to develop a new waveform.

The Valleylab waveform is a modulated waveform that originates as a coagulation current, unlike "blend current," which is a modulated cut current waveform. Using the adaptive properties of the ESU, the voltage of the new waveform is controlled such that there is less tissue drag than with pure coag current, but improved hemostasis as compared with pure cut current.

So now, surgeons who are accustomed to electrosurgical pencils with only 2 buttons (yellow for cut and blue for coagulate) now may use a third button for application of this new Valleylab waveform.

Surgeon-controlled variables

Choosing the color of button or pedal to push is only one way that the surgeon can impact how electrosurgical instruments can affect what happens at the tissue level. Other variables include electrode size and shape, contact with tissue as energy is applied, and length of time of energy administration.

The effect that energy has on tissue is quite different, for example, if a surgeon uses a needle electrode rather than a ball electrode. With the former, the electrons are concentrated at the needle tip and as they are discharged, they rapidly create heat and tissue separation. At the same wattage setting with the ball electrode, tissue desiccation is more likely than dissection because the electrons are widely distributed across the surface of the ball.

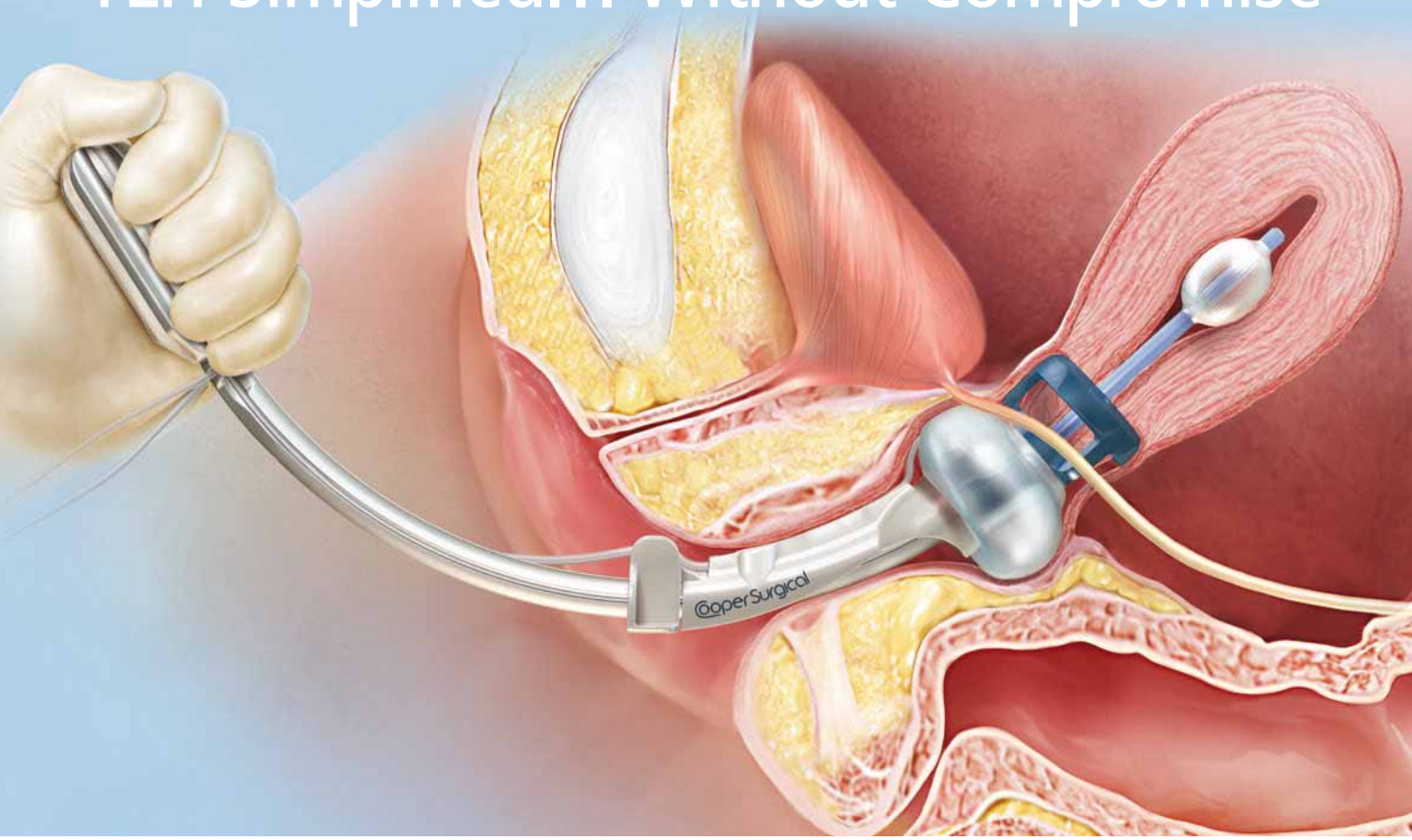
Likewise, if a surgeon moves the instrument rapidly, penetration is more superficial than the deep penetration that would occur if the instrument were held in place or moved slowly. So the surgeon controls many variables that can impact what he or she sees at the tissue level when operating with monopolar electrosurgical instruments.

Thermal injury

Surveys have shown that up to 18% of surgeons have experienced a thermal injury complication during laparoscopic surgery.[3,4] A significant portion of the shaft of the typical laparoscopic electrosurgical instrument is not visible on the video monitor, creating a potential for unrecognized injury. Instrument insulation failure and direct and capacitive coupling can cause stray energy burns. All of these are more likely to occur with the use of a high-voltage waveform (coagulation current).[1]

A capacitor is created when an insulator (eg, the coating of the shaft of an instrument) separates 2

TLH Simplified… Without Compromise



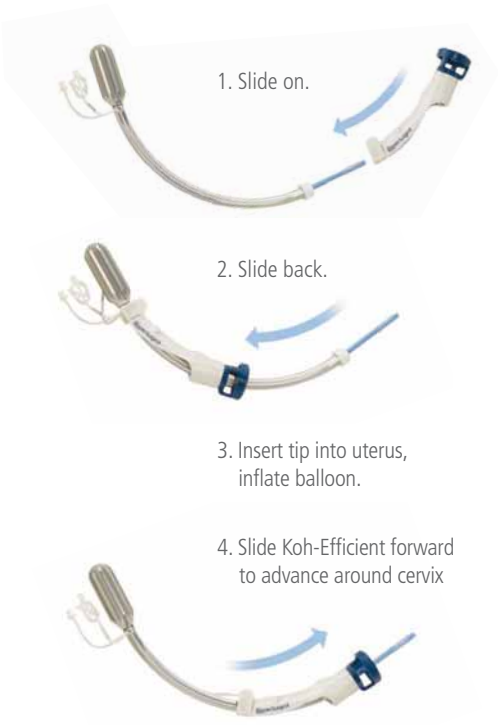


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FIGURE 2 THUNDERBEAT platform

The THUNDERBEAT platform incorporates ultrasonic technology into the lower blade and bipolar tissue desiccation between the jaws.

conductors (eg, the metal conductor inside the shaft and a metal laparoscope). If enough energy is stored within this capacitor, it can discharge spontaneously. "Open-air-activation" can also contribute to this. Open-air-activation refers to activating the button or pedal before the electrode tip is near the target tissue. The result is accumulation of electrons along the electrode's surface, which can build up enough energy within the capacitor to produce a spontaneous discharge to surrounding structures, resulting in injury.

Insulation failure is more difficult to predict and the most common cause of electrosurgical energy-related thermal injury.[4] Montero et al found evidence of insulation failure in 19% of reusable and 3% of disposable instruments used in cholecystectomy instrument sets at 4 hospitals.[5]

A technology referred to as active electrode monitoring (AEM) is designed to detect both insulation failure and capacitative coupling. By integrating a coaxial conductive shield into the shaft of the instrument and running that through the AEM monitor, the system can detect insulation failure and deactivate the ESU before energy is delivered (Figure 1).

Although the adaptive properties of modern ESUs have minimized but not eliminated risk of capacitative coupling by reducing potential high-voltage peaks, this is true only in instruments with intact insulation.

With the growing government focus on reducing complications, there may be increased interest in maximizing risk reduction. This may result in a growing interest in technologies such as AEM that are currently available but not very well known because of limited marketing.

Strategies that can help reduce the potential for stray monopolar energy injuries include using low-voltage waveforms (cut current) and lower wattage settings, avoiding open-air-activation, and using AEM instrumentation.

FIGURE 3 LigaSure Advance

The LigaSure Advance from Covidien incorporates both bipolar and monopolar technologies. The jaws compress the tissue and a seal is created using bipolar energy. The pedicle can be cut using a blade. The electrode at the tip of the instrument utilizes Covidien's new Valleylab waveform.

Bipolar versus monopolar instruments

In general, risk of unrecognized thermal injuries is lower but not completely eliminated with use of bipolar electrosurgical instruments. A traditional Kleppinger-style bipolar instrument creates a great deal of lateral thermal spread. In fact, that is what a surgeon requires in order to achieve effective tubal desiccation during laparoscopic sterilization. Such thermal spread, however, may be undesirable when the instrument is being used to control uterine vasculature in an area adjacent to the ureter.

The modern generation of bipolar vessel sealer/cutting devices uses the adaptive technology present in today's ESUs to deliver controlled, low-voltage energy with very minimal lateral thermal spread. Currently available advanced bipolar devices on the market in the United States include the PlamaKinetics System, LigaSure, EnSeal, and Caiman. Each of these devices is approved to seal and cut tissue pedicles up to 7 mm in diameter. Some of these instruments include the THUNDERBEAT platform from Olympus, which integrates both ultrasonic and advanced bipolar technologies (Figure 2). The LigaSure Advance incorporates both advanced bipolar and monopolar technologies (Figure 3). The Caiman 12 Plus offers an articulating 12-mm instrument (Figure 4).

Strictly speaking, electrosurgery is defined as the interaction of electrons with tissue to achieve a desired clinical effect. As with monopolar instruments, bipolar instruments generate heat within the tissue

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FIGURE 4 **Caiman 12 Plus**

The Caiman 12 Plus articulating vessel sealing instrument. The 50-mm jaw length first compresses the tissue pedicle and then uses bipolar energy for the tissue seal. The pedicle is then mechanically transected with a blade.

pedicle via the interaction of the electrons within the tissue itself delivered via alternating current (AC).

The Altrus Thermal Tissue Fusion system fits that definition but it is not an electrosurgical instrument, although it uses electricity to create heat that in turn achieves the desired tissue effect. In contrast with true electrosurgical instruments, the Altrus system uses direct current (DC) to heat the jaws of the instrument and then passively transfer that heat to the tissue (Figure 5). No electricity enters the patient through the device. The system monitors the temperature at the jaws and then bladelessly cuts through tissue. It comes in both 10-mm and 5-mm options.

The PlasmaJet system is not strictly an electrosurgical device either, but use of direct current electrical energy is necessary to eventually create the heat needed to treat tissue. In the case of this system, a beam of argon gas is energized when it passes through a low DC voltage that is applied between internal bipolar electrodes. This separates the argon gas atoms into positive and negative ions and creates the fourth state of matter known as plasma.

The PlasmaJet system releases its energy in 3 ways: light, heat, and kinetic energy. The effect at the tissue level is influenced by how close the jet of ionized gas is to the tissue, which handpiece is chosen, and which button is pushed on the handpiece. The maximum depth of tissue penetration effect is only 2 mm, reached after 5 seconds of continuous application.

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Conclusion

Safe application of energy-based surgical devices lies in the hand of the surgeon. A sound understanding of the fundamentals of surgical practice is still of prime importance.

Adherence to standards for careful surgical dissection, appropriate exposure of the surgical field, and a thorough knowledge of anatomy are still necessary regardless of all of the advances in modern technology. COG

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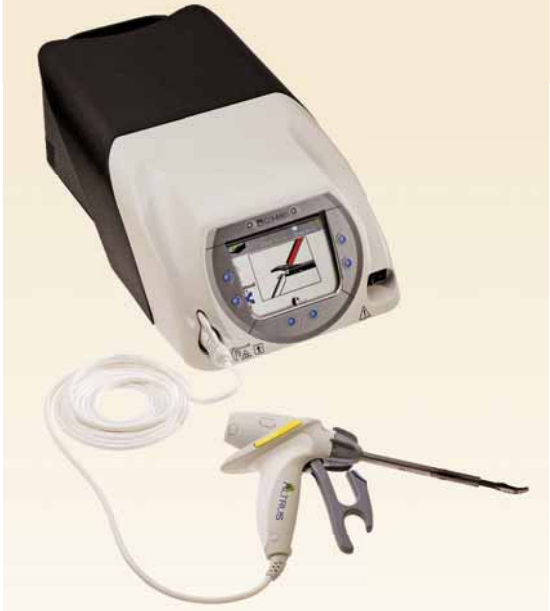
FIGURE 5 **Altrus system**



The Altrus system uses direct current to heat the jaws of the instrument and then passively transfer the heat to the tissue. The system monitors the temperature at the jaws and then bladelessly cuts through tissue.

Vaginal versus Laparoscopic Hysterectomy

Three surgeons discuss the pros and cons of the two methods.

VAGINAL HYSTERECTOMY

The best minimally invasive approach

By Rosanne M. Kho, MD

When a simple hysterectomy is indicated for a benign indication, evidence still indicates that the vaginal route is the route of choice. The latest Cochrane review on the surgical approach to the benign hysterectomy confirmed this from data gathered from 27 randomized trials that involved 3643 patients.[1] Compared to the abdominal approach, vaginal hysterectomy is significantly associated with improved outcomes including shorter length of hospital stay, faster return to normal activity, and less postoperative febrile morbidity.

When comparing vaginal to laparoscopic routes, evidence favors the vaginal approach. At the present time, standard practice guidelines are based upon the Cochrane review, which found that as a group, laparoscopic hysterectomies took longer to perform and were associated with more bleeding than were vaginal hysterectomies. In the Cochrane meta-analysis, laparoscopic hysterectomy took 54 minutes longer than vaginal hysterectomy (95% CI, 43.7–63.5). A subanalysis of laparoscopic versus vaginal hysterectomy found no significant differences in complications, although it included only 2 trials. It is from these findings that the authors went on further to state that laparoscopic hysterectomy should be considered only when vaginal access is not possible.

The available randomized trials evaluating complications between laparoscopic hysterectomy and vaginal hysterectomy show that there are no significant differences. The eVALuate study, involving 2 parallel randomized study arms—laparoscopic hysterectomy versus total abdominal hysterectomy and laparoscopic hysterectomy versus vaginal hysterectomy—found no difference in the complication rates after the 2 procedures in the vaginal trial (9.8% for laparoscopic hysterectomy, 9.5% for vaginal hysterectomy, mean difference 0.33%, -5.2% to 5.8%, $P = 0.92$; odds ratio 0.97, 0.52 to 1.81). This trial, however, was not powered to detect a difference and

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VAGINAL HYSTERECTOMY CONTINUED

its results, therefore, are inconclusive.

Total laparoscopic hysterectomy is thought to be superior to vaginal hysterectomy in its ability to provide better anatomical views and performance of concomitant procedures such as for excision of endometriosis. This is supported in the vaginal arm of the eVALuate study where additional pathology was diagnosed in significantly more patients undergoing laparoscopic hysterectomy (16.4%) than vaginal hysterectomy (4.8%) ($P = 0.01$). The practical significance of this finding, however, remains unclear. To date, we have no studies that evaluate differences in re-operation rates or patient satisfaction scores.

More recently, a meta-analysis was performed that included only RCTs comparing total laparoscopic hysterectomy and vaginal hysterectomy for benign disease.[3] This study involved 5 studies (not included in the Cochrane Review) and 332 patients. This meta-analysis confirms previous findings that total laparoscopic hysterectomy takes longer to perform than vaginal hysterectomy (on average by 30 minutes), and similarly, found no significant difference in the rate of any complication, short-term or long-term, between vaginal hysterectomy and total laparoscopic hysterectomy.

It also found that total laparoscopic hysterectomy was associated with less postoperative pain and decreased length of hospital stay. The authors of this meta-analysis admitted serious limitations to their conclusions including: 1) 3 out of the 5 studies were of moderate methodological quality and 2 were of poor quality; 2) statistical heterogeneity and bias were noted in some of the study outcomes including those of postoperative pain and complications; and 3) the meta-analysis is severely underpowered to detect for rare complications such as lower urinary tract injuries. Given these major limitations, conclusive statements cannot be made and the findings of this meta-analysis should only be interpreted with caution.

> "The vaginal route should be approached first for benign hysterectomy **whenever feasible.**"

It is important to note that, though rare, vaginal cuff dehiscence can be a devastating complication that is notably less in vaginal hysterectomy compared to total laparoscopic hysterectomy.[4] Ted Lee's group found that the relative risk of vaginal cuff dehiscence after a total laparoscopic hysterectomy compared to vaginal hysterectomy was 21, a significant difference between the two groups.

A cost-effectiveness analysis undertaken with the eVALuate data revealed that the vaginal approach was more cost-effective compared to the laparoscopic route primarily due to the use of disposable instruments in laparoscopy.[5] Laparoscopic hysterectomy costs an average of $708 more per patient than vaginal hysterectomy. With still more than 500,000 hysterectomies performed annually in the United States, the vaginal approach is most relevant at this time of cost containment.

In conclusion, based on evidence, current guidelines advocate that the vaginal route should be approached first for benign hysterectomy whenever feasible. To clarify differences in postoperative pain, patient satisfaction, and return to normal activity, we are still in need of better quality studies to compare vaginal hysterectomy and total laparoscopic hysterectomy. Until these studies become available to reveal otherwise, vaginal hysterectomy remains the route of choice for its advantages with less operative time and cost. COG

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Important Safety Information continued

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Pregnancy Considerations
- The Essure procedure should be considered irreversible. Patients should not rely on Essure inserts for contraception until an Essure Confirmation Test [modified hysterosalpingogram (HSG)] demonstrates bilateral tubal occlusion and satisfactory location of inserts.
- Effectiveness rates for the Essure procedure are based on patients who had bilateral placement. If Essure inserts cannot be placed bilaterally, then the patient should not rely on Essure inserts for contraception.
- Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated.
- Pregnancies (including ectopic pregnancies) have been reported among women with Essure inserts in place. Some of these pregnancies were due to patient non-compliance or incorrect clinician interpretation of the Essure Confirmation Test (modified HSG).

Procedural Considerations
- Perform the Essure procedure during early proliferative phase of the menstrual cycle. Terminate procedure if distension fluid deficit exceeds 1500cc or hysteroscopic time exceeds 20 minutes as it may signal uterine or tubal perforation. Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity due to risk of fractured insert, fallopian tube perforation or other injury.
- DO NOT perform the Essure procedure concomitantly with endometrial ablation. Avoid electrosurgery on uterine cornua and proximal fallopian tubes without visualizing inserts.

Nickel Allergy
Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.

MRI Information
The Essure insert was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-05.

Clinical Trial Experience
- Safety and effectiveness of Essure is not established in patients under 21 or over 45 years old, nor in patients who delivered or terminated a pregnancy less than 8-12 weeks before procedure. Women undergoing sterilization at a younger age are at greater risk of regretting their decision.
- The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain, and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain, and dyspareunia.

This product does not protect against HIV infection or other sexually transmitted diseases.

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LAPAROSCOPIC HYSTERECTOMY

The new gold standard

By Ted Lee, MD and Cara R. King, DO

The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion #444, "Choosing the Route of Hysterectomy for Benign Disease," states that vaginal hysterectomy is the approach of choice whenever feasible.[1] In cases in which vaginal hysterectomy is not indicated or achievable, laparoscopic hysterectomy serves as an alternative to abdominal hysterectomy.

Many of us who routinely perform minimally invasive surgery are glad that our professional society has finally acknowledged what we have known all along: Abdominal hysterectomy should be minimized.

Vaginal hysterectomy has consistently been considered the gold standard when it comes to a minimally invasive approach to hysterectomy. This has not changed over the years despite the introduction of a laparoscopic technique.

In the most recent study by Wright et al., abdominal hysterectomies continued to account for 41% of all hysterectomies in 2010, whereas laparoscopic hysterectomy accounted for 30%, vaginal hysterectomy for 20%, and robotic assisted hysterectomy for 10% of all hysterectomies.[2]

One of the reasons behind the slow adoption of laparoscopic hysterectomy during the past decade may be that many gynecologists did not readily recognize the benefits or feasibility of laparoscopy. Of course, this is not the only reason that laparoscopic hysterectomy was not adopted more widely. For many years after its introduction, laparoscopic hysterectomy was ridiculed by mainstream ob/gyn academicians. Until recently, recruiting faculty with expertise in advanced laparoscopic surgery was rarely a priority for most US ob/gyn department chairmen.

> "Patients who undergo laparoscopic hysterectomy consistently have **lower pain scores.**"

There are multiple reasons why vaginal hysterectomy has consistently been considered the gold standard in minimally invasive approaches to hysterectomy. A primary advantage is that with no abdominal incisions, it is undeniably the most cosmetic among the different types of hysterectomies. It is also the least costly of the different types of hysterectomies.[3]

However, this cost margin is greatly reduced when reusable instruments are implemented and the average length of stay for laparoscopic hysterectomies is taken into account. The decreased length of stay for laparoscopic hysterectomies as compared to vaginal hysterectomies is largely attributable to reduced postoperative pain. Several trials comparing postoperative pain in laparoscopic and vaginal hysterectomies have shown that patients who undergo laparoscopic hysterectomy consistently have decreased pain scores.[4,5]

Operative time and complication rates are additional comparative measures that have been used to critique these 2 minimally invasive approaches. In the meta-analysis by Gendy et al, laparoscopic hysterectomy was found to take longer than vaginal hysterectomy;[6] however, significant heterogeneity was found between trials. In general, operative time is largely surgeon- and team-dependent.

In regard to complication rate, current literature has found no significant difference between these 2 modalities.[5] Earlier studies that found significantly higher rates of complications associated with laparoscopic hysterectomy did not take into account the natural learning curve associated with the application of a novel procedure.

Vaginal surgery has inherent limitations, including anatomical factors and underlying disease states. It is interesting to note that all of the randomized trials within the meta-analysis performed by Gendy et al listed similar exclusion criteria.[6]

Furthermore, even if a vaginal route is feasible, specific underlying comor-

LAPAROSCOPIC HYSTERECTOMY CONTINUED

bidities make it an inappropriate technique. Using endometriosis as an example, a vaginal approach would preclude an adequate evaluation of the pelvis and make complete excision of endometriosis impossible. Essentially, there are exquisitely few limitations in terms of hysterectomy complexitin the hands of a skilled laparoscopic surgeon; however, limitations exist innately in vaginal surgery despite excellent surgical skill.

An additional reality that must be acknowledged is that many residents are not graduating with surgical competency in all hysterectomy techniques. The Accreditation Council for Graduation Medical Education guidelines require that obstetric and gynecology residents perform at least 15 total vaginal hysterectomies prior to graduation.[7] This scant minimum is quite difficult to achieve for many residents; Tu et al found that on average, teaching hospitals are performing only 13% of their hysterectomies vaginally.[8]

In addition, it has been found that residents require approximately 21–27 vaginal cases to gain competence.[9] In fact, when questioned, only 41.7% of 2011 graduating residents reported vaginal hysterectomy as their preferred route of hysterectomy, as compared to 47.1% who preferred laparoscopic approaches.[10]

Ideally, all gynecologists should be proficient in both laparoscopic and vaginal hysterectomies. In reality, this expectation is simply not possible in the context of current ob/gyn training and clinical practice. Efforts to promote both vaginal hysterectomy and laparoscopic hysterectomy will ultimately only contribute to the slow decline of abdominal hysterectomy.

Considering its versatility, laparoscopic hysterectomy should be the new gold standard in minimally invasive approaches. Professional societies such as ACOG and AAGL should direct more of their resources to promote education in and practice of laparoscopic hysterectomy if a substantial decrease in abdominal hysterectomy is truly our primary goal. COG

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VIDEO

See *Contemporary OB/GYN* Deputy Editor Dr. Jon I. Einarsson moderate a discussion on this topic between **Dr. Ted Lee** and **Dr. Rosanne Kho**. Visit **http://www.aagl.org/cobgyn**

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BY **BRIAN A. LEVINE, MD, MS,**
AND **DAN GOLDSCHLAG, MD, FACOG**

Consumer tech brings big changes for 2014 and beyond

New apps, hardware, and software bring powerful functions to patients and physicians.

Many of the technologies that will define 2013 have just recently been released. In this Tech Tools installment we introduce you to consumer-level technologies that have the ability to transform the way that we practice ob/gyn and the way our patients interact with us.

Apple iPhone 5S

Announced: September 10, 2013
http://www.apple.com/iphone-5s

One of this year's most highly anticipated technological announcements came nearly one year after its predecessor, iPhone 5.

The newest Apple flagship iPhone iteration, the iPhone 5s, shares the same design and screen resolution of the iPhone 5, but is completely redesigned. iPhone 5s features Apple's newest processor, the 64-bit A7 chip, a dedicated motion co-processor dubbed M7, a fingerprint scanner also known as Touch ID, as well as a dramatic improvement in battery life and a slew of new camera features (hardware- and software-related).

For those of us who depend on our phones for more than entertainment and basic communication, each iteration of the iPhone has included new features that have improved our daily workflow. With the introduction of LTE (high-speed data for mobile phones) to the iPhone 5, many of us gained the ability to remotely access our network with a relatively quick connection.

While to the average consumer the iPhone 5s may seem like an incremental improvement, this model does more for medicine than any other upgrade.

With the introduction of the 64-bit A7 processor, this device will have more than 50 times the graphics performance of the original iPhone while having more than 40 times the processing power. This new processor will allow software developers to add features to their mobile EHR applications and likely add significant functionality to their smartphones.

The proprietary M7 motion co-processor will integrate data generated by the iPhone's built-in accelerometer, gyroscope, and compass. Apple describes the co-processor's technology as a chip that "knows when you're walking, running, or even driving." This proces-

Learn about the Glow fertility & conception app on page T26

sor will allow for the rapid collection and utilization of spatial information. It will be interesting to see how software developers will take advantage of this chip, but it appears that this information will be invaluable for those who want to capture fitness-related information, whether it be data derived from the device or collected from a wearable device.

The M7 processor will also afford the iPhone the ability to accurately navigate delicate spaces—think GPS for a room. For patients who are sight-limited or visually impaired, the iPhone 5s may be able to help map an office, a house, or a room, and guide users as they perform their daily activities.

While the fingerprint scanner, Touch ID, may seem like a gimmick, this may be the one reason to invest in a new device.

As many of us merge our work device into our home device, security is of paramount importance. Through the integration of a proprietary fingerprint scanner into the "home button," the iPhone 5s has the ability to scan subepidermal skin layers to recognize your fingerprint with 360° readability. Not only will Touch ID allow you to access your phone faster (since now you have the option of just placing your finger on the button instead of typing in a code), but it will also allow for true user authentication.

Although Apple states that the fingerprint information will not be available for other apps nor will it be stored in the cloud, it is possible that third-party software developers could create apps that would take advantage of the fingerprint scanner, and thereby allow for single-step login to either a remote connection or an EHR. Having the ability to "tap-to-sign" an order, acknowledge a result, or simply log in would be a huge improvement in smartphone workflow, and would likely save countless hours for those of us who try to be self-sufficient from the palms of our hands.

In sum, the iPhone 5s has a familiar form, shares our favorite current iPhone features, and finally takes a huge leap forward in helping healthcare providers disconnect from their desktops/laptops.

Samsung Galaxy Gear

Announced: September 4, 2013
http://www.samsung.com/global/microsite/galaxynote3+gear/

Not since the advent of Dick Tracy's 2-Way Wrist Radio in 1946 has there been so much excitement about what can be done on the real estate of a person's wrist. Many manufacturers have experimented with multifunction watches and have integrated calculators, GPS, altimeters, and emergency transmitters. However, no company has taken the step of creating a device with mass-market appeal that permits a watch to be an extension of the smartphone.

Earlier this year we saw the release of the Pebble Smart Watch, which allows users the ability to view text messages and other notifications, accept or decline incoming calls, and control simple phone features. Samsung, Apple's most formidable competitor, took the giant leap in creating a mass-market device that exhibits the principle of form following function.

Although this device in its current iteration can only be paired with the soon-to-be-released Samsung Galaxy Note 3, it sports an impressive 800 MHz processor and 512MB of RAM, which is far superior to the power of any full-sized desktop computer only a few years ago. The Gear is designed to focus the user on the most salient features of the phone and help the user access critical notifications/alerts, utilize certain applications (70 will be available at the time of launch), play music, or even take photos. The Gear also has an integrated microphone to allow the user to navigate the watch or

phone by using just his or her voice.

It is not hard to imagine the utility of discreet paging/messaging while seeing patients—it is more polite to look at your watch than it is to pull out your device in the middle of a patient interaction.

With smartphone EHR integration, it likely will be possible to receive critical notifications about patients (laboratory values, test results, etc.) while your phone is in your pocket. And best of all, if you misplace your phone, the Gear smart-watch has the ability to activate your phone's alerts and help you find it.

While the Galaxy Gear may not be a standalone device, it gives Android users and Samsung addicts the first taste of multidevice synced technology; the potential for practicing medical professionals is huge.

Glow

Announced: August 8, 2013
https://glowing.com/

Glow is a fertility-tracking, conception-planning iPhone app co-written by Max Levchin, a co-founder of PayPal. Unlike any other fertility-focused smartphone app, Glow has an intuitive, simple user interface and is 100% free.

After the user enters simple information such as last menstrual period and length of cycle, the Glow engine generates a personalized calendar that shows the user her next fertile window and a 5-day view that shows the chance of conceiving on any given

day. The application also lets the user enter her partner's contact information so that the couple can be "synced" and alerted for when they should be "trying."

A future Glow app may allow physicians to connect with their patients through the app. As more users subscribe, the Glow team will collect the data that users enter into the program. Using this crowd-sourced data, the Glow team will improve the accuracy of their algorithms.

On September 22, the Glow team introduced Glow Genius. Beyond the features described above, the program now has a new tool called "Insights," which gives patients personalized daily fertility-related facts. With every log and completed task, the user will see new information on how her actions have affected her "quest to conceive."

Glow Genius now has charts to help patients track their cervical mucus and basal body temperature so they will know when they are about to ovulate. It can also be set to remind patients when to "try" or to restock their prenatal vitamins.

The optional Glow FIRST fund is a crowd-funded fertility program. As part of the $50/month optional program, those users who do not get pregnant after 10 months will receive financial credits to undergo an infertility evaluation or even treatment.

Projects Mighty & Napoleon

Announced: September 17, 2013
http://xd.adobe.com/mighty/notify.html

Adobe, the software manufacturer of Photoshop and Acrobat, is now going to start manufacturing consumer-level hardware. Their soon-to-be-released products—Project Mighty, a cloud-connected e-pen, and Project Napoleon, a digital-hybrid ruler—will forever change how we interact with our tablets.

Project Mighty is an iPad stylus that works with Adobe's Creative Cloud app (cloud-based software that lets users carry and work on drawings across multiple devices). The Bluetooth-powered pen has pressure sensors that emulate the experience of writing on physical paper. Unlike a traditional pen, Project Mighty has a button that lets the user toggle between different pen/pencil tips, ink styles, and colors.

Project Napoleon is a digital ruler that the user physically places on top of an iPad. It projects guidelines onto the screen, allowing the user to draw precise lines and edges for artwork or architectural projects. When the pocket-sized ruler launches later this year, it will be released with 2 drafting applications that harmoniously work with Projects Mighty & Napoleon.

It is important to recognize the potential for these 2 gadgets in medicine. They will allow physicians to annotate figures, hand-write notes in charts, or document findings from a physical exam or surgical procedure.

It may be possible to create schematics of surgical approaches, annotate radiographic studies, and improve the tablet-based experience for medical students.

Structure Sensor

Announced: September 17, 2013
http://www.occipital.com/

Occipital has created a truly disruptive technology. There is no other device like the Structure Sensor: It is the first 3D sensor for mobile devices.

The Structure Sensor is a consumer-level strap-on device that lets an iPad become a highly sensitive and accurate 3D mapping device. The sensor seamlessly attaches to the back of an iPad, is self-powered with an internal battery, and connects via the standard iPad cable.

The potential uses for a device like this are boundless. It's not hard to think of a number of potential medical applications. Beyond configuring your next office/clinic to help improve your workflow efficiency, the device can be used to measure human dimensions.

It's possible that orthopedic surgeons will be able to fit prostheses in ways never before possible; audiologists will be able to make more comfortable hearing aids; weight-loss programs will be aided by precise body dimensions; and fundal-height measurements will be replaced with volumetric 3D renderings.

Summary

This year we're seeing consumer-level devices capable of professional applications.

Although medicine may not be in the forefront of every manufacturer's product plans, it only takes a little creative energy to turn almost any device into a health-tech tool. COG

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AAGL HIGHLIGHTS

A DON'T-MISS MEETING FOR SURGEONS

AAGL is set to have its 42nd annual global congress in Washington, DC, November 10-14. Highlights of the meeting include an opening address by Neil Martin, MD, Chair of Neurosurgery at UCLA; surgical tutorials; innovation forums; an interactive course on laparoscopic teamwork; and 3 hours of live telesurgery sessions.

Female surgeons can join Barbara S. Levy, MD, for a breakfast on Tuesday, November 12. Following the breakfast, Dr. Martin will discuss the need to create clinical quality guidelines. The Congress's general session will be on endometriosis research. AAGL's honorary Chair, C.Y. Liu, MD, will give an address about his tenure and experiences with the organization.

The Congress will also feature the newly revived "Stump the Professors" contest. Three difficult cases will be presented to a panel of experts.

Surgeons with an interest in telesurgery have the opportunity to view 3 hours of surgery for continuing medical education (CME) credits. Topics will include cystectomy for endometrioma with maximum preservation of ovarian function, mini-laparoscopic treatment of endometriosis, single port robot-assisted laparoscopic total hysterectomy, and laparoscopic supracervical hysterectomy for large fibroids.

CME credits are available from postrgraduate courses, the Global Congress, the Jordan M. Phillips Keynote Address, and the General Session. Specialty courses are available in 5 areas of medicine: Urogynecology, Oncology, Reproductive Medicine/Endometriosis, Pelvic Pain, and Robotics. Simulation coursework covers laparascopic suturing techniques and office hysteroscopy and transvaginal ultrasound.

Attendees who are interested in a fellowship in minimally invasive gynecologic surgery (MIGS) should plan to attend the "Make Me a MIG Surgeon" session.

On the exhibit floor, be sure to visit the *Contemporary OB/GYN* booth (number 140).

Participants who are able to take a moment away from the Congress will have plenty of choices. Those who want to stay in the National Harbor area will find many attractions on the waterfront.

Attendees who want to go farther afield can take a short cab ride to Alexandria, Virginia to trace George Washington's footsteps, travel back to the 18th century by visiting King Street, or take a late-night ghost tour. Those who would like to visit the National Mall or Georgetown can take either a shuttle from the Gaylord National Resort and Convention Center or the National Harbor Water Taxi.

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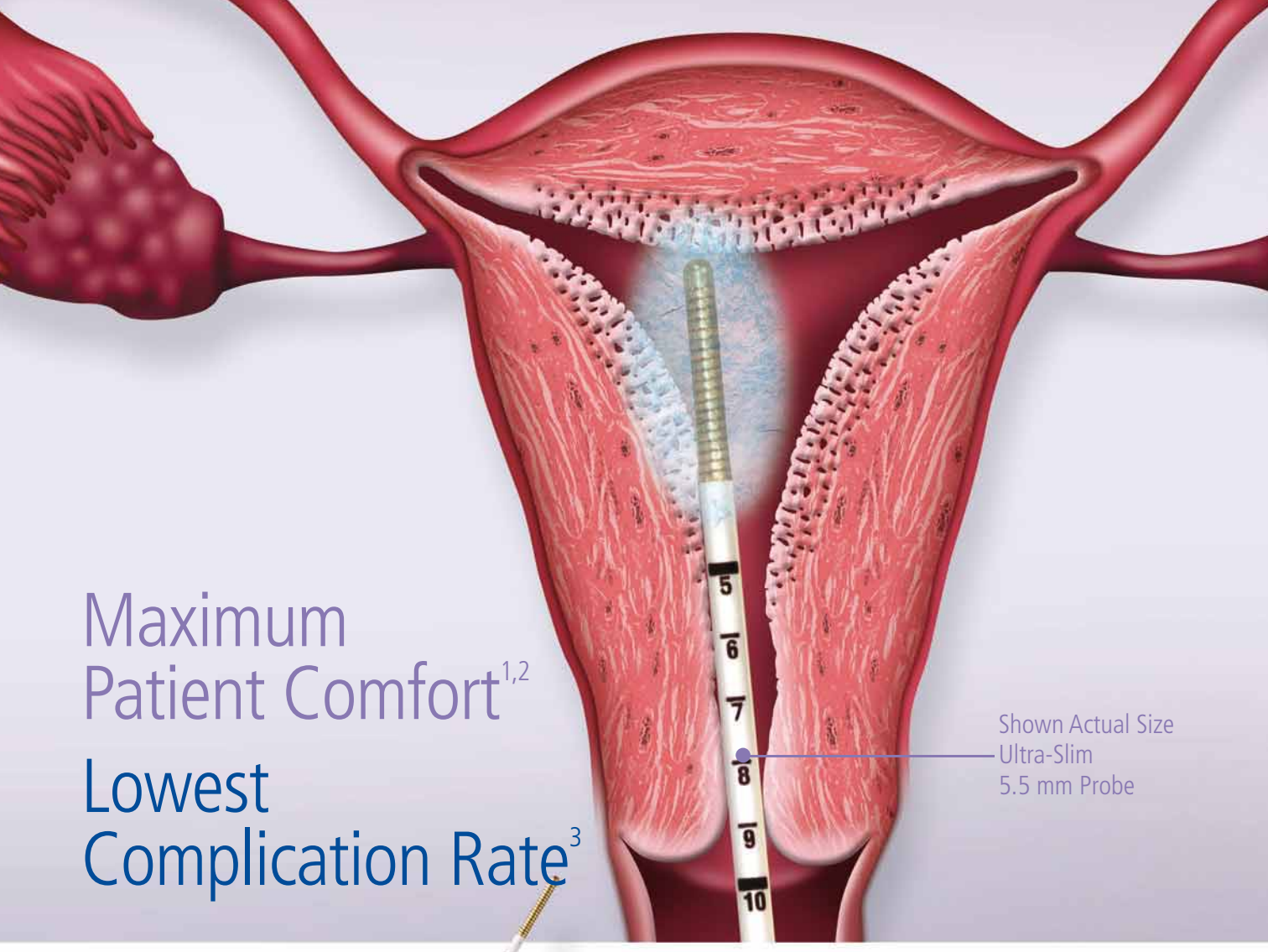

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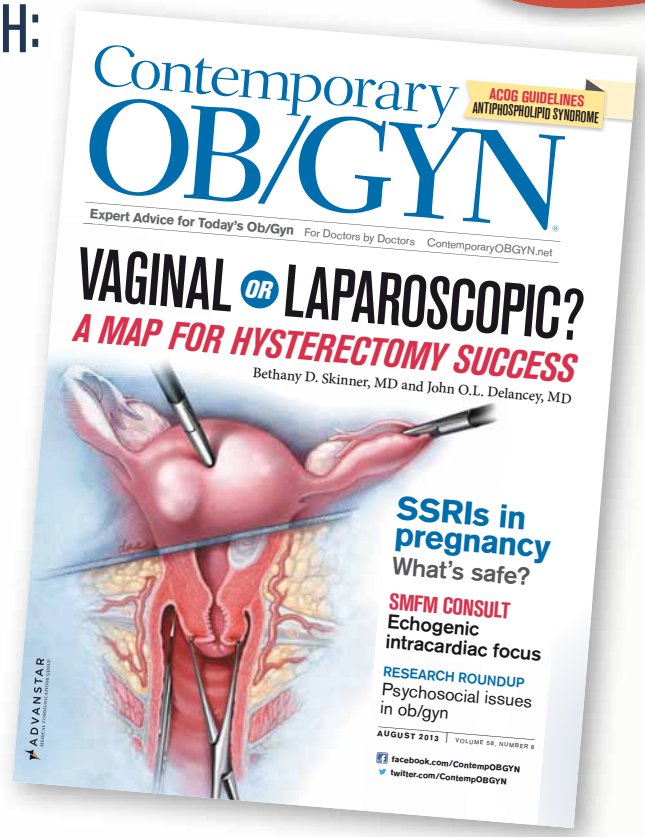

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Assessing nutritional needs in pregnant patients with prior bariatric surgery

A 31-year-old woman presents for a routine first prenatal appointment. She has had bariatric surgery.

Q What information does the ob/gyn need about this woman's bariatric surgery in order to best counsel her about nutrition in pregnancy?

A The obstetrician should determine the type of weight loss surgery that was performed. Bariatric surgery can cause weight loss through intake restriction, food malabsorption, or a combination of these. The 2 most common bariatric procedures performed in the United States in reproductive-age women are Roux-en-Y gastric bypass (65%) and adjustable gastric banding (24%).[1] Roux-en-Y gastric bypass restricts intake and food absorption, whereas adjustable gastric banding limits only food intake.

Other bariatric surgeries are performed but are much less common. Today, biliopancreatic diversion is rarely performed because it is associated with a higher mortality rate and more significant nutritional deficiencies.[2,3] Vertical banded gastroplasty and sleeve gastrectomy are both restrictive surgeries.

Q What nutritional deficiencies are obstetrical patients at risk for after bariatric surgery?

A Nutritional deficiencies are frequently encountered in patients who have undergone bariatric surgery and they can be amplified during pregnancy. Malabsorptive procedures are associated with more nutritional deficiencies than is restrictive surgery, as outlined in Table 1.[3] Nonpregnant patients who have had bariatric surgery are commonly prescribed a variety of nutritional supplements because of nutritional deficiencies. Table 2 outlines examples of some of these routine supplements.

When a patient who has undergone bariatric surgery becomes pregnant, a detailed history should be obtained at the first prenatal visit. Patients with prior bariatric surgery may have unique nutritional deficiencies that are not routinely considered in healthy obstetric patients. These deficiencies may cause health problems. Persistent complaints such as muscle pain or cramps, easy bruising and/or skin and mucosal changes in

TABLE 1 Variations in nutritional deficiencies by type of bariatric surgery

Nutritional Deficiency	Type of Bariatric Surgery	
	Malabsorptive (eg, Roux-en-Y)	**Restrictive** (eg, gastric banding, vertical banded gastroplasty, sleeve gastrectomy)
Malnutrition	At risk	Rare
Fat malabsorption	At risk	None
Vitamin B_{12}	At risk	None
Folate	At risk	None
Vitamin B_1 (Thiamine)	At risk	Rare
Iron	At risk	At risk
Fat-soluble vitamins (ADEK)	At risk	None

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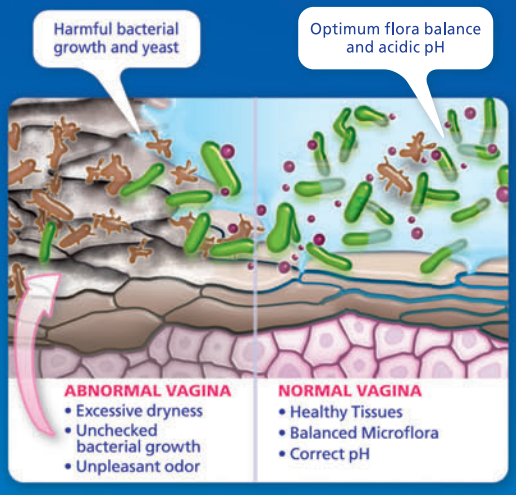

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a pregnant patient may be symptoms of vitamin or micronutrient deficiencies.[4] These may be more relevant if the patient is still in the rapid-weight-loss phase following her bariatric surgery.

Current guidelines suggest checking serum levels of vitamin B_{12} and folate during pregnancy in women with prior bariatric surgery,[5] along with a complete blood count, iron, ferritin, calcium, and vitamin D levels; measurement every trimester has been suggested.[6] Longitudinal nutritional data are not available or limited, however, regarding vitamin supplementation and other supplementation during pregnancy in women who have had bariatric surgery. Therefore, the recommendations are based on expert opinion.

Q Are there special considerations for nutrient replacements after bariatric surgery?

A In patients who have had bariatric surgery, stomach pH is altered and the surface area for absorption decreases. These changes may warrant manipulation in the preparation, route, or dose of nutrient replacements. Liquid or chewable vitamins are better absorbed than tablets.[7] Calcium carbonate depends on acid for absorption, whereas calcium citrate does not; therefore, calcium citrate is the recommended replacement.[8] Administration of iron simultaneously with vitamin C improves iron absorption because the vitamin C helps to acidify the stomach.[9]

Absorption of oral vitamin B_{12} depends on intrinsic factor produced by the parietal cells of the stomach, and production of intrinsic factor may be significantly altered when a part of the stomach is surgically removed. Therefore, even with adequate oral supplementation in a patient with malabsorptive surgery, a nutritional deficiency in vitamin B_{12} may not be corrected and intramuscular injections may be required.[4] Because of reduced drug absorption, periodic monitoring of nutritional levels is suggested to ensure adequate replacement.

TABLE 2 Suggested nutrient supplement and dose after bariatric surgery in nonpregnant adults*

Nutrient Supplement	Dose (per day)
Multivitamin[a]	1-2
Calcium citrate	1200-2000 mg
Vitamin D	400-800 IU
Folic acid	400 µg
Elemental iron[b]	40-65 mg
Vitamin B_{12}	350 µg orally or 1000 µg IM once a month

*These recommendations are derived from nonpregnant women[5] and there is a paucity of data on their role during pregnancy.
a. For pregnant women: 1 prenatal vitamin
b. For women of reproductive age

Q Are there special nutritional considerations for pregnant women who have had bariatric surgery?

A Some women with malabsorption resulting from bariatric surgery may have vitamin A deficiency. High levels of vitamin A intake have been associated with fetal anomalies.[9] Currently human evidence is insufficient to establish a safe threshold for daily intake. The maximum amount of vitamin A recommended for pregnant women is 8000 to 11,000 IU per day or not more than 5000 IU in supplements.[6,10]

Bariatric surgery patients are at particular risk of anemia, which is also common during pregnancy. If common causes of anemia like iron deficiency, vitamin B_{12} or folate deficiency, and hemoglobinopathy are excluded, clinicians should consider less-common causes of nutritional anemia, such as copper deficiency.

Q How should a pregnant woman with a history of bariatric surgery be followed throughout the pregnancy?

A Care should be taken when administering screening tests for gestational diabetes. In about 50% of patients who have Roux-en-Y gastric bypass, dumping syndrome can occur. It is characterized by symptoms including a shaky, sweaty, dizzy sensation accompanied by a rapid heart rate and, occasionally, by severe diarrhea.[11] Alternative methods, such as home glucose monitoring or hemoglobin A1C measurement, may be considered.

Summary

Patients who undergo bariatric surgery, especially malabsorptive procedures, are at increased risk of nutritional deficiencies (Table 1). Pregnancy may make some of these nutritional deficiencies more severe by increasing demand or decreasing intake, especially if a patient has nausea and vomiting. The evidence for monitoring of nutritional deficiencies and for supplementation is insufficient to make any strong recommendation, and more research is needed. Patients should continue to receive monitoring and supplementation as needed, in collaboration with the bariatric surgery team and medical specialists, and the ob/gyn should remain vigilant for signs and symptoms of nutritional deficiencies. With careful monitoring, women with bariat-

PATIENT HANDOUT

If you are pregnant or considering pregnancy after bariatric surgery

By the Society for Maternal-Fetal Medicine (SMFM) with the assistance of Dr. Michelle A. Kominiarek

What does my ob/gyn need to know about my bariatric surgery in order to care for my pregnancy?

Your obstetric provider will need to know what type of bariatric surgery you had. For example, was it a gastric bypass procedure, also known as a Roux-en-Y? Or did you have a banding procedure, also referred to as a gastric band? Your provider will also want to know if you had any complications from the procedure, such as second surgeries, blood clots, or blood transfusions.

Many women with irregular menstrual cycles start to have more menstrual regular cycles after bariatric surgery. The chances of getting pregnant increase after bariatric surgery. Most experts recommend waiting approximately 18 months after bariatric surgery before getting pregnant so that you can reach your weight loss goals before becoming pregnant. Therefore, it's important that you use contraception for the first 18 months after surgery. Studies have shown that women who get pregnant soon after their bariatric surgery can still have healthy pregnancies, but their obstetric providers may need to monitor their weight and nutrition more closely.

I am in my first trimester and I have lost weight.

Shouldn't I be gaining weight during pregnancy?

In general, pregnancy is a time for gaining weight, not losing it. Some women who had bariatric surgery do lose weight during pregnancy. If you are losing weight, your provider should review your food intake and may have you see a nutritionist. Blood tests may also be ordered. If you continue to lose weight or are simply not gaining weight, your provider may order more frequent ultrasounds to see if your baby is growing normally. Specific recommendations will be made based on your current weight.

I was diagnosed with anemia after my bariatric surgery. How will that be monitored during my pregnancy?

Many patients are anemic (have a low blood count) after bariatric surgery. Anemia is also common during pregnancy. Anemia can happen because your body is not getting enough nutrients or vitamins such as iron, vitamin B_{12}, or folate. Your provider can do blood tests to help determine why you are anemic. If your body needs more nutrients or vitamins, your provider will prescribe those that are right for you. Your provider may then repeat the blood tests to make sure your anemia is getting better. In addition, your provider will review your diet and may suggest certain foods that can provide some of the needed nutrients.

My bariatric surgeon recommended that I take a multivitamin daily. Are there any other vitamins or supplements that I should take now that I am pregnant?

In pregnancy, you should take one prenatal vitamin a day. If you are currently taking a multivitamin, you should switch to a prenatal vitamin, ideally before you get pregnant. The folic acid in the prenatal vitamin is important for your baby. You should not take other supplements unless your provider recommends them. After certain types of bariatric surgery, it is more difficult for the stomach or intestines to absorb nutrients and vitamins. If that is happening, your provider may recommend a vitamin that comes in a shot (injection) or is given through an IV (placed in your vein).

My last pregnancy was healthy, but that was before the bariatric surgery. Are there any other changes I should expect during my prenatal care?

Most pregnant women are screened for gestational diabetes at about 24 to 28 weeks of

pregnancy. If you have been pregnant before, you may remember drinking a sugary beverage to check for diabetes. This test can be difficult to take if you had a bariatric procedure like a Roux-en-Y gastric bypass, so your provider may recommend a different way to test for diabetes during pregnancy.

If you had a gastric band procedure, your provider may talk to you about what to do with the fluid in the band. The options are to keep the fluid the same, to remove the fluid, or even to put more fluid in. This is a procedure that your bariatric surgeon would do. You should talk to both your obstetric provider and your surgeon about which approach is best for you.

Some rare complications from bariatric surgery can occur at any time, including during pregnancy, and they can affect both you and your baby. Therefore, it is important that you tell your provider if you are having abdominal pain, nausea, or vomiting at any point during the pregnancy.

Bariatric surgery is not a reason to have a cesarean delivery. You should talk to your provider about which delivery option is best for you.

Can I still breastfeed even though I had bariatric surgery?

Yes. Breastfeeding is recommended, and your nutrition during that time is especially important. If you have low levels of nutrients or vitamins in your body, they can also be low in your breast milk, but that is rare. Your baby's health care provider should know if you have any nutrient or vitamin deficiencies so that your infant's growth and development can be monitored more closely.

Many women with prior bariatric surgery are still overweight or obese, which can delay lactogenesis (milk coming in). You may want to talk to a lactation consultant who can support you through breastfeeding and help you be successful with it.

COG To download a PDF of this patient education handout, go to www.contemporaryobgyn.net/pregnant_after_bariatric_surgery.pdf

ric surgery are likely to have normal pregnancy outcomes. COG

DR. JOHNSON is Professor, Department of Obstetrics and Gynecology, Medical University of South Carolina, North Charleston.

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†Please see adjacent page for details.

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References: 1. Data on file, Watson Laboratories, Inc. **2.** Generess® Fe full Prescribing Information, Watson Pharma, Inc. March 2012.

Generess® Fe is an estrogen/progestin combined oral contraceptive indicated for use by women to prevent pregnancy.

IMPORTANT SAFETY INFORMATION

Women who are over 35 years old and smoke should not use Generess® Fe. Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. Generess® Fe is contraindicated in pregnant patients, and those with a high risk of arterial or venous thrombotic disease, undiagnosed abnormal uterine bleeding, breast cancer or other estrogen- or progestin-sensitive cancer, liver tumors, or liver disease. Use of Generess® Fe should be stopped if a thrombotic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Generess® Fe should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. If jaundice occurs, Generess® Fe treatment should be discontinued. Generess® Fe should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. Women who are pre-diabetic or diabetic, should be monitored while using Generess® Fe. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia. Patients using Generess® Fe who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated. The most commonly reported adverse events associated with the use of Generess® Fe included nausea/vomiting, headaches/migraine, depression/mood complaints, dysmenorrhea, acne, increased weight, breast pain/tenderness and anxiety. **Generess® Fe will not protect against HIV infection (AIDS) or other sexually transmitted diseases.**

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Brief Summary

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WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke [*see Contraindications* (4)].

1 INDICATIONS AND USAGE

GENERESS Fe is indicated for use by women to prevent pregnancy.

The efficacy of GENERESS Fe in women with a body mass index (BMI) of > 35 kg/m² has not been evaluated.

4 CONTRAINDICATIONS

Do not prescribe GENERESS Fe to women who are known to have the following:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning,* and *Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.7)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.2)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3), Use in Specific Populations (8.7),* and *Clinical Pharmacology (12.3)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop GENERESS Fe if an arterial or deep venous thrombotic (VTE) event occurs. Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The excess risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop GENERESS Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start GENERESS Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop GENERESS Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

5.2 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use GENERESS Fe because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.3 Liver Disease

Discontinue GENERESS Fe if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.4 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop GENERESS Fe if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.5 Gallbladder Disease

Studies suggest the relative risk of developing gallbladder disease may be increased among COC users.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking GENERESS Fe. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking GENERESS Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue GENERESS Fe if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.8 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Patient diaries from the clinical trial of GENERESS Fe showed that on the first cycle of use, 37% of subjects taking GENERESS Fe had unscheduled

bleeding and/or spotting. From Cycle 2-13, the percent of women with unscheduled bleeding/spotting ranged from 21-31% per cycle. For those women with unscheduled bleeding/spotting, the mean number of days of unscheduled bleeding/spotting was 5.2 in the first cycle of use and ranged from 3.6 – 4.2 in cycles 2-13. A total of 15 subjects out of 1,677 (0.9%) discontinued the study prematurely due to metrorrhagia or irregular menstruation.

Women who are not pregnant and use GENERESS Fe may not have scheduled (withdrawal) bleeding every cycle or may experience amenorrhea (absence of any bleeding and spotting). The incidence of amenorrhea in the clinical trial increased from 8.1% of the subjects in Cycle 2 to 18.4% by Cycle 13. For those women who had scheduled (withdrawal) bleeding, the average duration of bleeding per cycle in Cycles 2-13 was 3.7 days.

If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. GENERESS Fe use should be discontinued if pregnancy is confirmed.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Women with a history of depression should be carefully observed and GENERESS Fe discontinued if depression recurs to a serious degree.

5.11 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs.

5.12 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.13 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and smoking *[see Boxed Warning,* and *Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial 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.

A phase 3 clinical trial evaluated the safety and efficacy of GENERESS Fe for pregnancy prevention. The study was a multicenter, non-comparative, open-label study with a treatment duration of 12 months (thirteen 28-day cycles). A total of 1,677 women aged 18-46 were enrolled and took at least one dose of GENERESS Fe.

Adverse Reactions Leading to Study Discontinuation: 8.5% of the women discontinued from the clinical trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were nausea (1.0%), weight increase (0.8%), acne (0.8%), metrorrhagia (0.7%), altered mood (0.4%), hypertension (0.4%), irritability (0.3%), migraine (0.3%), decreased libido (0.3%) and mood swings (0.3%).

Common Adverse Reactions (≥ 2% of all treated subjects): nausea/vomiting (8.8%), headaches/migraine (7.5%), depression/mood complaints (4.1%), dysmenorrhea (3.9%), acne (3.2%), anxiety symptoms (2.4%), breast pain/tenderness (2.4%), and increased weight (2.3%).

Serious Adverse Reactions: Hypertension, depression, cholecystitis, and deep vein thrombosis.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with GENERESS Fe.

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

7.3 Changes in Plasma Levels of Co-Administered Drugs

COCs containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of GENERESS Fe have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

GENERESS Fe has not been studied in postmenopausal women and is not indicated in this population.

8.6 Renal Impairment

The pharmacokinetics of GENERESS Fe have not been studied in subjects with renal impairment.

8.7 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic disease on the disposition of GENERESS Fe. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal *[see Contraindications (4),* and *Warnings and Precautions (5.3)]*.

8.8 Body Mass Index

The safety and efficacy of GENERESS Fe in women with a BMI > 35 kg/m^2 have not been evaluated.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives including ingestion by children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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Benefits and Risks of Sterilization

Female and male sterilization are both safe and effective methods of permanent contraception used by more than 220 million couples worldwide (1). Approximately 600,000 tubal occlusions and 200,000 vasectomies are performed in the United States annually (2–4). For women seeking permanent contraception, sterilization obviates the need for user-dependent contraception throughout their reproductive years and provides an excellent alternative for those with medical contraindications to reversible methods. The purpose of this document is to review the evidence for the safety and effectiveness of female sterilization in comparison with male sterilization and other forms of contraception.

COMMENTARY

Benefits and Risks of Sterilization: Considering all the options

By **Paula J. Adams Hillard, MD**
Dr. Hillard is Professor, Department of Obstetrics and Gynecology Stanford University School of Medicine, Stanford, California, and a member of the *Contemporary OB/GYN* Editorial Board.

Sterilization remains an important method of limiting family size, and is particularly popular in the United States. The landscape of both permanent and reversible contraception has changed since the 2003 version of the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on sterilization. Practice Bulletin Number 133: *Benefits and Risks of Sterilization*, replaces the 2003 Bulletin.

Rates of female sterilization increased dramatically in the 1970s, peaked in 1977, were stable through the 1980s and early 1990s, but have declined since. More recently, use of long-acting reversible contraception (LARC) including intrauterine devices (IUDs) and the subdermal implant has increased; these methods are comparable to sterilization in efficacy, but are reversible and do not require a surgical procedure.

Hysteroscopic sterilization involving the placement of a metal coil in the tubal ostia (Essure) was approved by the US Food and Drug Administration (FDA) in 2002. A second hysteroscopic method (Adiana) was also approved, but it is no longer manufactured for financial reasons related to a patent infringement suit. ACOG issued a committee opinion in 2010 (reaffirmed in 2012) on the use of hysterosalpingography (HSG) after tubal sterilization to emphasize the difference between hysteroscopic sterilization and female sterilization by other means.[1]

In the case of hysteroscopic sterilization, women must be counseled to use interim contraception for at least 3 months after the procedure and to have an HSG done at that time to confirm bilateral occlusion. A specific HSG protocol requiring lower filling pressure is indicated, and if occlusion is still not documented, a repeat HSG must be performed 3 months later. Logistical issues such as scheduling challenges and changes in insurance coverage undoubtedly contribute to failure rates with this type of sterilization procedure. Adherence rates to the follow-up HSG range from 13% to approximately 70%. Nonetheless, there are advantages to an office procedure with minimal anesthesia and a short recovery period.

Weighing benefits and risks

Challenges to the performance of immediate postpartum sterilization remain, including insurance coverage and logistical issues involving scheduling and availability of anesthesia and operating rooms. The Practice Bulletin

calls for physicians to be advocates for our patients to address these and other potential barriers.

As rates of cesarean delivery increase, the option of concurrent sterilization should be addressed during prenatal care. The potential for relatively easy partial salpingectomy at the time of cesarean delivery makes informed forethought and decision-making imperative. Because serous ovarian cancer may arise from tubal precursor lesions, salpingectomy may be not only a more effective method of sterilization than occlusive methods, but it also may prevent future disease. Additional data are required to weigh the benefits and risks of this surgical approach.

The benefits, risks, efficacy, and alternatives for all contraceptive options need to be discussed with patients, including the alternative of immediate post-placental or post-abortion insertion (or intrauterine placement) of an IUD, which has an efficacy comparable to sterilization. While this procedure is relatively infrequently performed in the United States, it is growing in popularity as an easier alternative to surgical sterilization. The higher rates of expulsion associated with this option (compared with the interval insertion procedure) must be weighed against the logistical benefits for women.

Vasectomy is a contraception option that all couples who consider their families to be complete should consider. Because it is an office procedure performed with local anesthesia, it is safer, more effective, and less expensive than abdominal approaches to female sterilization. However, physicians must inform couples that it is not immediately effective; it takes 3 to 6 months for men to become azoospermic. Thus interim contraception is required.

Sterilization vs LARCs

Female sterilization remains far more effective than other contraceptive methods such as combined oral contraceptives, which depend on daily consistent and correct adherence. Sterilization is also more effective than the patch, ring, injections, and barrier methods. However, the equation changes with LARC methods, which have failure rates comparable to female sterilization.[2] The levonorgestrel intrauterine system has considerable noncontraceptive benefits for heavy menstrual bleeding and pelvic pain. Women with those conditions should carefully weigh their decisions with regard to sterilization vs LARC methods.

As we help patients to understand the safety of contraceptive options, we must remember that although tubal occlusion lowers the overall risks of pregnancy, if a pregnancy does occur, it is more likely to be ectopic. This is not news to ob/gyns, but we must inform our patients about this potential risk and help them put the risk in perspective.

Concerns regarding post-tubal syndrome, with increased risks of abnormal bleeding after sterilization (a topic of discussion during my residency training years), have been put to rest.[3]

Since my residency (and due in significant part to the post-residency work of one of my fellow residents, Bert Peterson, MD), data from the US Collaborative Review of Sterilization (CREST), a large, prospective, multicenter observational study of more than 10,000 women, now make clear that failure rates for sterilization are higher than had originally been appreciated. The CREST study showed that sterilization failures vary by both age at sterilization and the method used.[4]

The study also found that the risks of pregnancy accumulate over time, and that for women aged 18 to 27 years, failure rates can be as high as 5% with bipolar coagulation and the spring clip.[4]

There are noncontraceptive benefits to sterilization; tubal occlusion reduces the incidence of ovarian cancer and the risk of acquiring pelvic inflammatory disease.[5]

Although young age is associated with an increased risk of regretting sterilization (in the CREST study, regret was expressed by 20.3% of those aged 30 and younger vs 5.9% for those older than 30),[6] the 2013 Bulletin strongly concludes that for a well-informed woman, age and parity should not be barriers to sterilization. However, the Bulletin notes that patients should be well informed about all contraceptive options, and in particular, they should be informed that LARC methods are at least as effective as tubal occlusion and are associated with lower morbidity and mortality. COG

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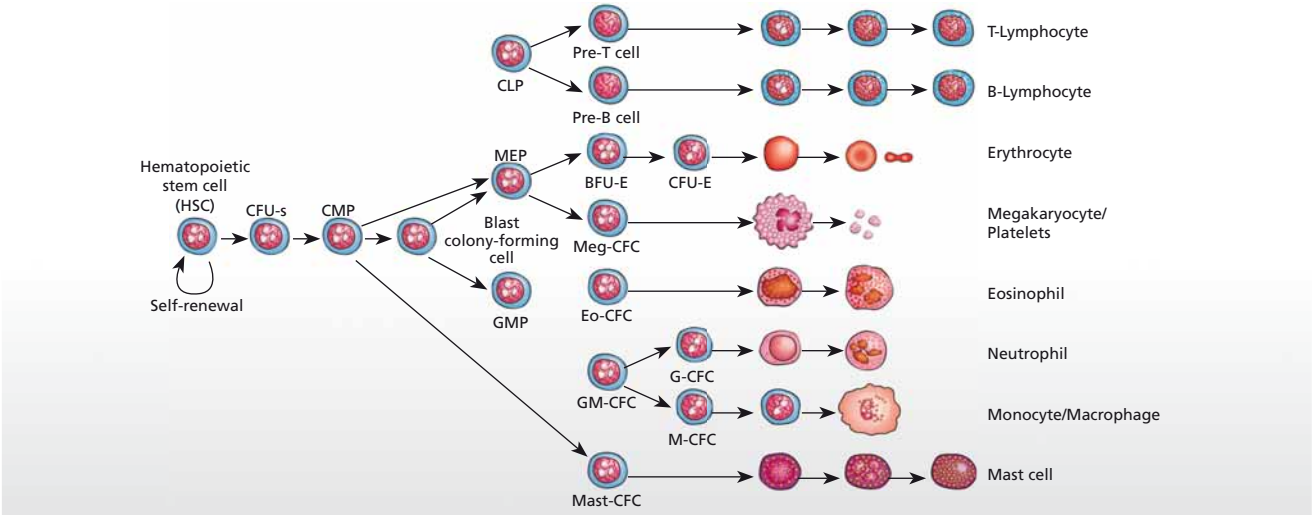
Much of his current research is focused on the characterization and utility of mesenchymal cells harvested from the perivascular region of the human umbilical cord.

Paving the Way: Cord Blood and the Autologous Newborn Stem Cell Banking Resource Paradigm

In the two decades since Umbilical Cord Blood Stem Cell (CBSC) banking was initially established, more than 1 million children have had their own CB cryopreserved in Private, also known as Family, Cord Blood Banks. Notwithstanding the use of such cells in transplantation medicine, particularly sibling transplants, this large stem cell reservoir represents a unique source of autologous CBSCs for the experimental treatment of children for acquired diseases such as Cerebral Palsy[1], Traumatic Brain Injury (TBI)[2], Type 1 Diabetes (T1D)[3], Hearing Loss[4], and idiopathic Autism Spectrum Disorder (ASD)[5]. These conditions are acquired at reasonably high frequencies in newborns and children (1/100-1/5,000)[6-10]; and, if determinations of significant clinical efficacy (i.e. improvements in clinical outcomes relative to cross-over, placebo-based controls) are achieved in such studies, cell-based interventions using banked autologous CBSCs and potentially HLA-matched allogeneic CBSCs, may greatly accelerate the use of this unique reservoir of cells in numerous applications of regenerative medicine.

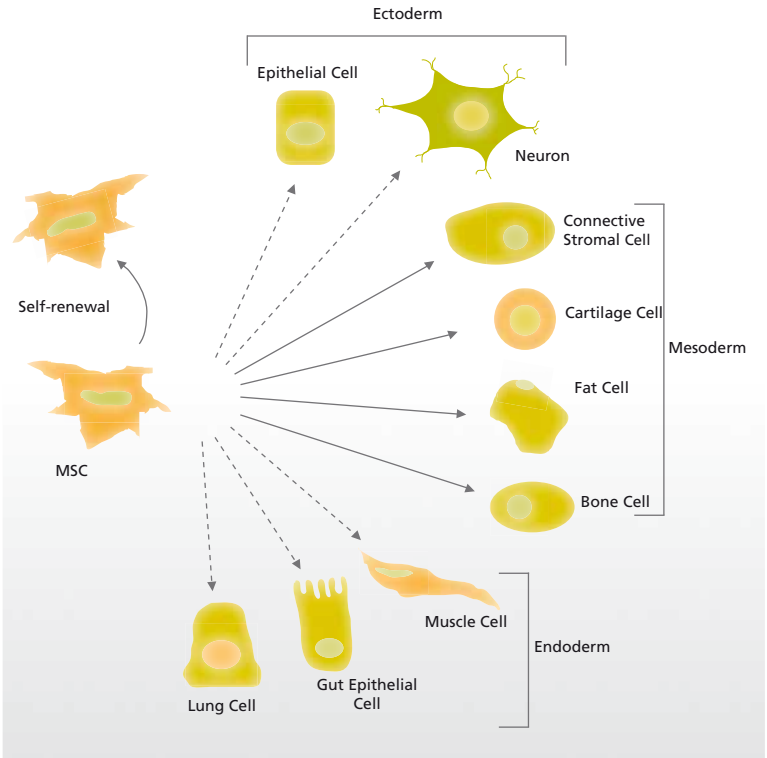
Figure 1. A diagram of the hematopoietic hierarchy. *Metcalf D. Stem Cells.* 2007;25:2390-2395. Adapted with permission.



The Next On-Ramp: Newborn Mesenchymal Stromal Cells

A second wave of newborn "stem" cell banking is now underway as more parents are choosing to cryogenically store cells from the Umbilical Cord Tissue (UCT). The structure of the human umbilical cord comprises several tissue types including the endothelial lining of the vessel and two arteries (these also contain residual CBSCs), the smooth muscle walls of the vessels, the Wharton's Jelly that supports the vessels, and the outer amniotic membrane. UCT therefore comprises cells of endothelial, mesenchymal and ectodermal origins, and represents a rich source of cells and, particularly in the perivascular Wharton's Jelly, a very rich source of mesenchymal cells. Collectively, these cells are called Tissue Stromal Cells (TSC) or, for the cells of mesenchymal origin, Mesenchymal Stromal Cells (MSC[12]). These newborn cells are entirely distinct from, but complimentary to, CBSCs in terms of their potential applications.

Figure 2. A diagram of the mesenchymal hierarchy. Figure adapted from Uccelli A., Moretta L., Pistoia V., 2008. "Mesenchymal stem cells in health and disease" *Nature Reviews Immunology* 8, 726-736.



This article will examine the potential utility of this unique source of cells, either alone or in combination with CBSCs, as therapeutics in a variety of important clinical indications. Similar to the model of clinical development enabled by autologous CBSC banking, this nascent opportunity is predicated on the availability of a distinct reservoir of autologous cells from the UCT of newborns. The list of potential acquired diseases that may one day be addressed with such cells is exhaustive and includes those related to the attenuation of autoimmunity in diseases such as Type 1 Diabetes and Rheumatoid Arthritis, as well as those related to the reversal of damage from a large number of degenerative diseases related to bone, cartilage, skin, muscle, nerve, liver, lung, muscle, pancreas and other endocrine tissues.

UCT therefore comprises cells of endothelial, mesenchymal and ectodermal origins, and represents a rich source of cells and, particularly in the perivascular Wharton's Jelly, a very rich source of mesenchymal cells.[11]

Understanding the Signage: Know Your Way Around Stem Cell Jargon

Why is there an interest in Newborn Stem Cells when other sources of cells, embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), or those from either babies' teeth or adult fat, or bone marrow, are so often touted as coming to the therapeutic rescue? As the adage goes, "thumbs are not fingers, fingers are not thumbs; toes are neither fingers nor thumbs. However, fingers, thumbs and toes are all digits". So, too, one might describe stem cells. In other words, ESCs are not HSCs, HSCs are not ESCs; MSCs are neither ESCs nor HSCs. However, HSCs, ESCs and MSCs are all "stem" cells. There are two very important points to be made here. First, as discussed above, each cell population is heterogeneous (cell populations extracted from any tissue are never only one phenotype – except perhaps ESCs). As an example, cord blood cells are often called cord blood stem cells or even hematopoietic stem cells, although the vast majority of cells within such a population are not true stem cells but may facilitate the functional potency of the stem cell pool. Similarly, mesenchymal cells derived from various tissues have been called "mesenchymal stem cells" (MSC) although the majority of cells within such a population are not true stem cells, which has given rise to the more general term "mesenchymal stromal cell" (also abbreviated to MSC). Second, the tissue origin, number, and potency, among other characteristics of each cell population, are indicative of the clinical therapeutic potential of said population.

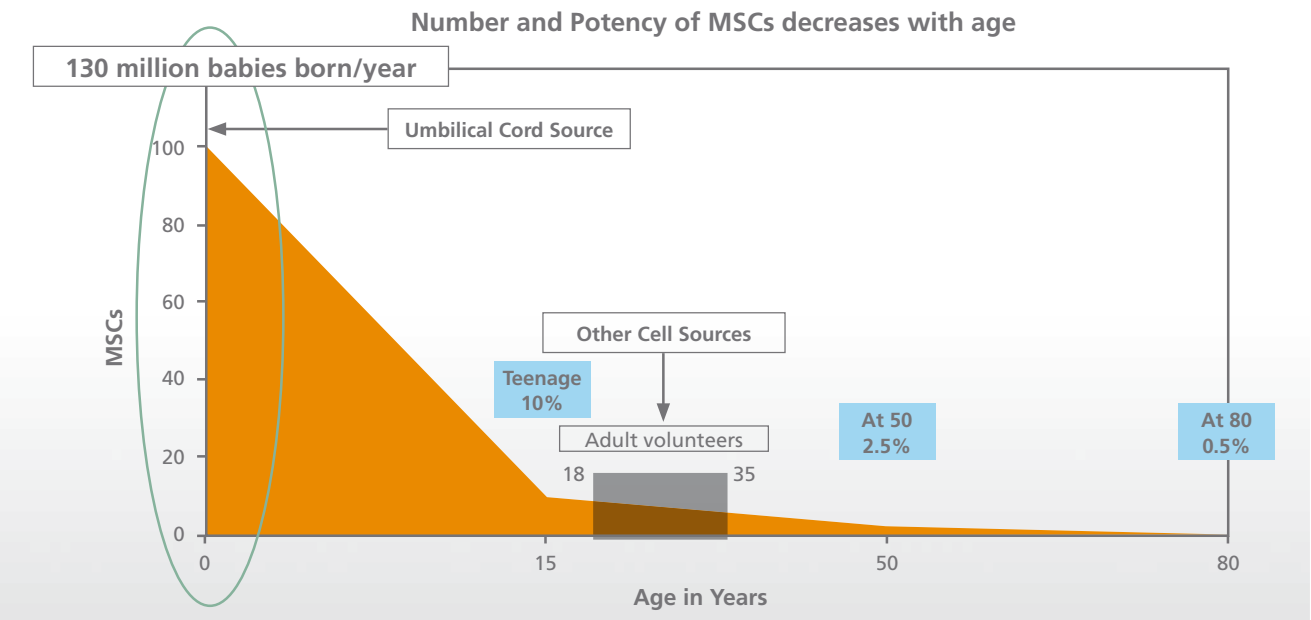
For example, ESCs, which are isolated from the inner cell mass of the blastocyst, are pluripotent stem cells capable of forming all tissues and organs of the body and uniquely capable of producing an entire individual as has been demonstrated with the cloning of Dolly.[13] Unfortunately, this does not bode well for the clinical applications of ESC since, in addition to the ethical debate about sourcing cells from embryos, there is a risk of the cells forming tumors in patients. The formation of teratomas is largely due to genetic programing or epigenetic coding, which locks the developmental pathway and does not permit ESCs the luxury of knowing what they want to be when they grow up. Doing so (i.e. maturing prematurely, so to speak) would restrict the inherent and natural pluripotent properties of these embryo-specific building blocks. To make a specific point, the use of ESCs to rescue a patient from radio-chemotherapy would be completely inadvisable, as ESCs do not readily form hematopoietic, or blood forming, constituents as they do not directly contribute to "definitive hematopoiesis" until well after primitive embryogenesis and the formation of the aorta-gonad-mesonephros (AGM) or yolk sac.[14]

Similarly, iPSCs are generally adult cells that have been induced or "reprogrammed" to form embryonic-like stem cells, and have garnered considerable attention in recent years, mainly due to the potential of reducing ethical concerns associated with stem cell research on embryo-derived cells. In fact, iPSCs form embryonic-like cells, and concerns regarding the quality of such cell lines with respect to their genomic integrity, epigenetic state, pluripotency and differentiation potential are well advised. These

are adult cells that knew what they were but are now reprogrammed to an embryonic-like state where, yet again, they are in a state where they don't know what they want to be! This is undoubtedly exciting science, but iPSC lines expectedly share the same hallmark as ESCs in that they generate teratomas in animal models. It is for this reason that most iPSC development today is focused on drug development *in vitro*, rather than the development of clinical therapies. It is noteworthy that CBSCs are between 10-100 times more efficient at making iPSCs than other cell sources[15]; likely due to their precise stage of developmental ontogeny.

At the other end of the spectrum are adult sources of "stem" cells (see comment above on "stromal cells") such as those acquired from Bone Marrow (BM) or Adipose (fat) tissue (AT). BM, for instance, contains many cell types including both HSC and MSC. Indeed, both BM and AT provide very heterogeneous cell populations with low concentrations of true stem cells and with limited potential. Nevertheless, this diversity results in an ability to generate products of each of the three germ layers (i.e. endoderm, ectoderm and mesoderm), giving the heterogeneous population some pluripotentiality. In colloquial terms, these adult-derived stem cells already know what they want to be when they grow up and it is very difficult, some might say inefficient, to coax them otherwise. Furthermore, as the figure below shows, there is a dramatic reduction in the relative number of MSCs available in the bone marrow of an individual as a function of their age.[16] Hence the prospect of obtaining therapeutic doses of stem cells from adult tissue sources rapidly diminishes as one ages. Perhaps an even more important issue is that adult cells have been shown to be less physiologically active than neonatal cells[17,18], and thus represent less potent therapeutics, which represents a key

Figure 3. Number and potency of MSCs decreases with age. Figure adapted from Caplan A., 2009. Why are MSCs therapeutic? New data: new insight. *J Pathol*; 217: 318–324.



advantage to be gained from storing neonatal cells for future use.

Various other tissues, including the pulp tissue of baby teeth and menstrual fluid, have been reported as sources of stem cells but may have limited immediate therapeutic value. For example, preservation of baby dental pulp cells cannot provide enough cells to treat a patient systemically or even enough cells to address local tissue pathologies without considerable expansion *ex vivo*. On the other hand, while menstrual fluid has been shown to be a rich source of various cells, its aseptic collection and storage is not without logistic difficulties. *Ex vivo* expansion for clinical use may be feasible in principle, but is often quite impractical under the current treatment paradigm offered by banking services, largely because such strategies involve extensive manipulation of cell products, and thus may be costly to produce and not available to customers at the time of need.

Perhaps an even more important issue is that adult cells have been shown to be less physiologically active than neonatal cells[17,18], and thus represent less potent therapeutics, which represents a key advantage to be gained from storing neonatal cells for future use.

Although each source of cells, including newborn stem cells, has its limitations, a confluence of factors makes the collection and storage of newborn stem cells following the birth of a child an extremely attractive option. With CBSCs, this continuum is well understood and includes the following features:

1. Ethically acceptable—avoidance of embryonic sourcing
2. Low risk of collection to mother and baby
3. Do not form teratomas
4. Enable relaxed matching requirements due to their immunological naiveté
5. Generate lower incidences of Graft versus Host Disease (GVHD) as is well established in transplant literature[19]
6. Readily accessible in a cryopreserved state with established stability over long periods of time[20]
7. Relatively high potency on a per cell basis when compared with alternative sources[21]
8. Relatively inexpensive and safe when compared with the harvest of Bone Marrow or Mobilized Peripheral Blood[22]
9. Regulatory environment favorable to established models of Public and Family banking models[23]
10. Potential for use in acquired disorders including Cerebral Palsy[24], Type 1 Diabetes[25], Hearing Loss[26], Traumatic Brain injury[27] and Autism Spectrum Disorder[28].

However, CBSCs are limited, particularly for use in reconstituting the blood and immune system following chemo-radiation treatment regimens for hematological malignancies in adults, since dose is related to body weight. Public banking services

have reduced this limitation, to some extent, by pre-selecting for large CBSC collections prior to cryopreservation so that transplant physicians can treat patients with greater body weight. In addition, advancements in the preparation and delivery of CBSCs, such as *ex vivo* expansion[29] and facilitated homing[30] to improve efficiency, are expected to alleviate dose limitations in the future, or perhaps enable the use of much smaller units in larger patients.

Importantly, families bank CBSCs predominantly for use in their children and/or adolescents so size limitations are not necessarily a problem, especially with respect to the use of CBSCs for the treatment of diseases where early intervention in relatively young children would be advised. An example of this is the Phase I clinical trial conducted at Duke University that treated 184 children with autologous (i.e. their own) CBSCs. Three quarters of the children treated in the trial were 3 years old or younger. Only 14% of these children had autologous cord blood units that would have qualified for Public Banking based on unit size, yet 94% of them received units meeting the minimal cell dose criterion.[31] Obviously, had those units been discarded at birth, the vast majority of these children would not have had the option of participating in the study.

It should be emphasized that the utility of a newborn's umbilical cord tissue cells is still somewhat speculative at this time, but certain features of this CT-MSC source parallel those of CBSCs, largely due to their similar availability and developmental ontogeny. For CT-MSCs, these advantages include:

1. Ethically acceptable—avoidance of embryonic sourcing
2. Low risk of collection to mother and baby
3. Relaxed matching criteria compared to cord blood
4. Immune modulating, i.e. attenuate immune reactivity
5. Establishment of stability and accessibility over long periods of cryopreservation likely
6. Relatively high potency on a per cell basis when compared with alternative sources
7. Relatively inexpensive and safe when compared with harvest from alternative sources
8. Regulatory environment favorable to established models of Public and Related banking models
9. Potential for use alone or in combination with CBSCs for diseases similar to and diverse from those currently addressed in studies using CBSCs.

Limitations of CT-MSCs have not been identified, to date, due to the current lack of knowledge related to cell dose, in vivo potency, route of delivery and many other factors. Notwithstanding these limitations, the spectrum of diseases currently being treated with MSCs from various tissue sources is vast, with the immune modulatory, anti-inflammatory and angiogeneic properties of these cells being the prime drivers for most clinical therapeutic indications chosen.

Would You Give Your Kid a Car Without an Airbag?: Treatment-Ready versus Segment Storage

One of the key advantages of harvested and stored CBSC is that, once thawed, they are ready to be used clinically, or are "treatment ready;" this means the cell product has been minimally manipulated, as practiced in tens of thousands of patients receiving CB transplants and hundreds of children receiving infusions of treatment-ready autologous CB in regulated FDA clinical studies. The same can be true for cells harvested from umbilical cord tissue. Indeed, in the newborn stem cell banking model, minimal manipulation may be the best current choice because the cells can be provided as a "treatment-ready" composition upon thaw, similar to CB. This is not the case where cord tissue, or CT-segments, are offered for storage as this approach cannot provide a "treatment-ready" option as the tissue must be further prepared after thaw to access any residual TSCs for infusion, and thus cannot be "minimally manipulated." In addition, a further disadvantage of simply storing segments of cord tissue is the poor resulting recovery of cells upon thawing of the tissue, as discussed in more detail below; an exception to this is the special technique of cryopreservation of the umbilical cord vessels and their surrounding perivascular tissue[32]. It is therefore imperative to distinguish between collection, processing and storage options provided by various Family banking operations for CT or CT cells. This section will describe the key elements required to ensure that families who choose to bank their newborn's CT-MSCs achieve their expectations of storing something of value. This is important as parents will reasonably expect to gain the maximum therapeutic value from their investment.

Anatomically, while the Wharton's Jelly comprises mesenchymal cells, the true mesenchymal stem cell (MSC) population is found in the Wharton's Jelly immediately surrounding the blood vessels of the newborn's umbilical cord—the so-called Perivascular Tissue. The richness of this source of MSCs can be demonstrated by established laboratory tests known as Colony-Forming Unit assays and Proliferation assays, which are measures of stem cell potency.[33] For reference purposes, the frequency of similar stem cells found in bone marrow is reported to be 1/10,000-100,000[11], while the perivascular region of the cord contains upwards of 1/300 such cells based on these well-established assays.[34] By contrast, banking operations offering to extract cells from the periphery of the Wharton's Jelly and surrounding amniotic epithelium will, by reference to the diagram below, start with significantly less tissue at much poorer cell density than that which can be derived from the perivascular tissue.

Figure 4. Schematic of human umbilical cord cross-section. Green dots represent cells; all other structures are as indicated. Schugar RC, et al. High harvest yield, high expansion, and phenotype stability of CD146 mesenchymal stromal cells from whole primitive human umbilical cord tissue. *J. Biomed. Biotechnol* 2009;2009:789526. Adapted with permission

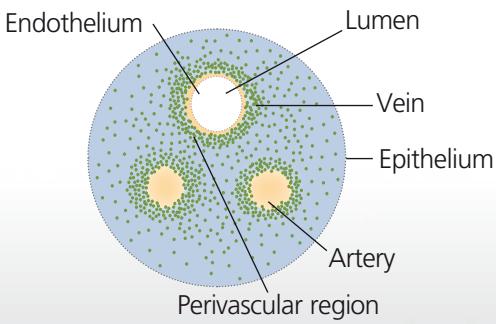
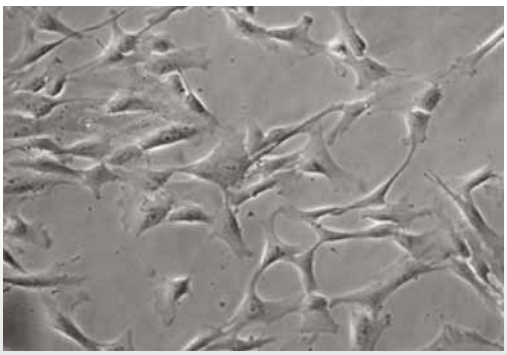


Figure 5. Perivascular cells from the umbilical cord display a fibroblastic morphology in culture (field width = 660 µm). Modified from Sarugaser R, et al. (2005) Human umbilical cord perivascular (HUCPV) cells: a source of mesenchymal progenitors. *Stem Cells*, 23(2):220-9.

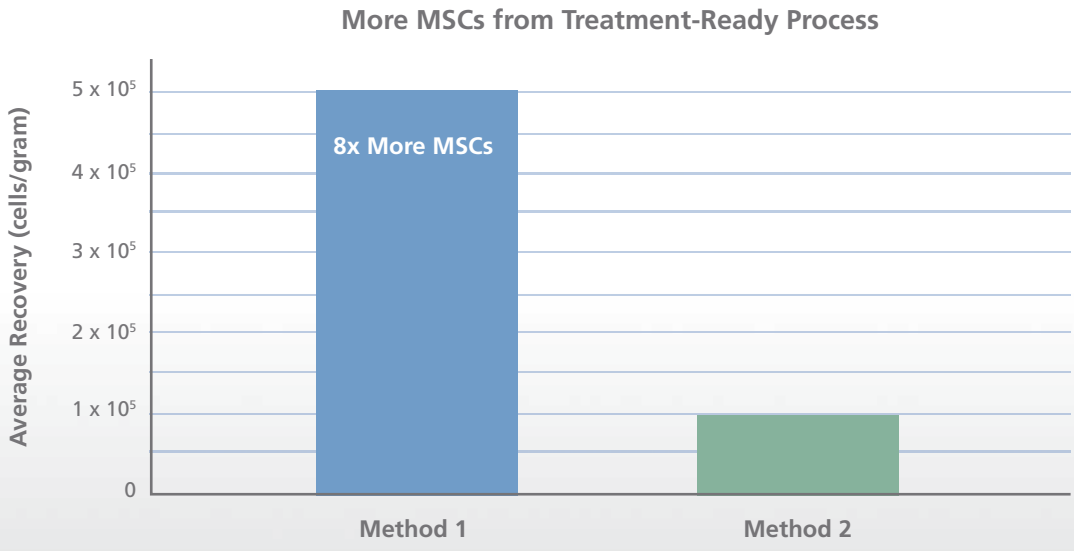


In addition, it has been shown that CT-MSCs are best isolated from the UCT prior to cryopreservation by digestion with the enzyme collagenase[35]. The cryopreservation of whole or segmented UCT, or the isolation of stem cells from CT *after* cryopreservation, is not advisable and may result in an up to 8-fold loss of the MSC fraction.[36]

Parents should seriously question the validity of those technologies offered by commercial banks that just freeze tissue as they will receive no guarantee that at a time of need the CT-MSCs will actually be available for use. The reasons are the following. First, as just mentioned, there may be no viable cells available upon thaw of the tissue segments. Indeed, some have reported that it is not possible to extract viable cells from frozen umbilical cords[37]. Second, even if cells can be recovered from frozen cord segments, the loss during cryopreservation can be significant, and

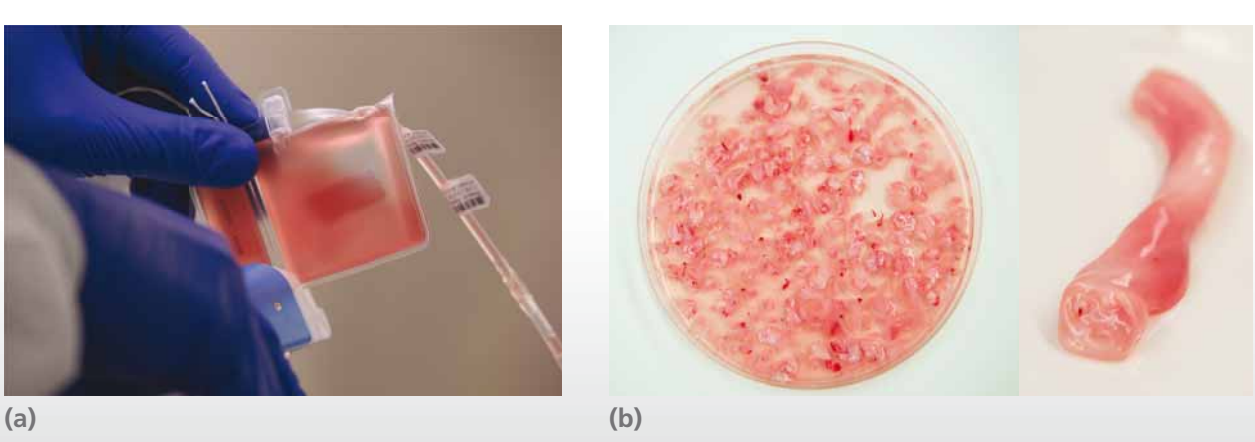
The cryopreservation of whole or segmented UCT, or the isolation of stem cells from CT *after* cryopreservation, is not advisable and may result in an up to 8-fold loss of the MSC fraction.[36]

Figure 6. Impact of cord tissue processing on cell recovery. Briddell R, Litkenhaus F, Foertsch G, et al. Recovery of viable MSCs isolated from fresh umbilical cord tissue, measured after cryopreservation, is on average 8-fold higher when compared to recovery of viable MSCs isolated from previously cryopreserved umbilical cord tissue [abstract]. *Blood* (ASH Annual Meeting Abstracts). 2011;118:Abstract 4398. Adapted with permission.



likely due to the impact (or more appropriately the lack of impact) of dimethyl-sulfoxide (DMSO), or cryopreservative, which is used in the step immediately prior to cryopreservation. Cryopreservation is a technique where the cyropreservant must penetrate the cells efficiently to preserve them for later use. Essentially, DMSO is an anti-freeze employed to protect the cells from freezing damage. This process, if done correctly, allows cells to be stored for many years. Such is the case with cryopreserved CBSCs, which is a cellular composition in liquid suspension, where maintenance of cellularity and potency after more than two decades of storage in liquid nitrogen conditions has been demonstrated.[38] Penetrating cryoprotectants like DMSO operate by increasing the solute concentration within cell cytoplasm to alleviate potential damage from ice crystal formation at, or near, the glassy state (approximately -146C). Such cryoprotectants are only effective if the time of exposure is limited (as they are extremely toxic to cells at ambient temperatures), but long enough to effectively penetrate cells. DMSO toxicity and penetration are both functions of time. For CBSC, the time exposure to DMSO is tightly controlled at or near 15 minutes, and this assures the DMSO solute has had enough time to penetrate the cells but not so much time as to become toxic before the cells are frozen. This is not the case with segmented CT since the very volume of tissue removes the possibility of precise control over the penetrating behavior of the DMSO. As a result, the cell population within the tissue may not receive adequate DMSO and valuable cells within the tissue are damaged in the freezing and thawing cycle. The better alternative is to cryopreserve the CT-MSCs as a suspension, similar to the methodology used in cryopreserving CBSCs. In this manner, the cells can be expected to remain intact for decades, if not the lifetime, of an individual, just as is the case with CBSCs or the frozen vessel technology referenced earlier[27]. Finally, patients electing to store CT-MSCs should investigate companies providing storage services to ensure the appropriate licenses are in place to enable access to stem cells in the tissue, either prior to or after storage.

Figure 7. Comparison of treatment-ready cord tissue with segmented and unprocessed umbilical cord tissue. (a) An 80/20 cryopreservation bag containing MSCs extracted from fresh umbilical cord tissue using a treatment ready processing method, ready for storage. (b) Segmented and unsegmented umbilical cord tissue.



Culture expansion of CT-MSCs is certainly feasible and may be advisable in specific indications, but additional complexity in manufacturing, regulatory and other concerns make this approach unlikely in a broad class of first-order therapies (i.e. those that impact one patient and require one unit for treatment), in which a child may benefit from the use of their own MSCs and there are no alternative sources of stem cells fitted for the treatment of the specific indication. In this scenario, even if expansion of CT-MSCs after thawing is desired, it would take significant expense in GMP manufacturing efforts to generate therapeutic compositions. Companies offering CT storage without prior isolation of cells may suggest that this is a trivial task, but may also offer no remedy for this deficiency in the event the units are requested for use.

Autologous CT-MSC storage/banking is now commercially available and a subset of parents are receptive to banking such stem cells for their future potential but, as mentioned earlier, the clinical utility of this unique source of newborn CT-MSCs has not been established. Establishing clinical utility in one or more key indications is an important component in the further commercialization of CT-MSC banking and the derivation of unique therapeutic strategies, such as treating haploidentical related or unrelated patients with newborn CT-MSCs, or combining CT-MSCs with CBSCs in transplants to support engraftment or infusions to support regeneration.

Where the Rubber Meets the Road: Putative Applications of CT-MSCs in Models of Disease

Historically, the clinical utility of CB was first established in sibling transplants, then allogeneic transplants and now great effort is underway to establish the utility of autologous CBSCs in acquired diseases. Unlike CBSCs, which differentiate into blood and immune-forming cells, the newborn's CT-MSCs have been shown in numerous independent studies to have the capacity to differentiate into bone[39], nerve[40], muscle[41], and endocrine[42] phenotypes, regulate immune responses[43], and functionally repair or reconstitute relevant animal models of disease[44]. As will be discussed later, these and other studies using alternative sources of MSCs would indicate that the administration of autologous MSCs, alone or in combination with CBSCs for acquired diseases, may be highly beneficial in any number of indications.

While the clinical utility of CT-MSCs remains to be established, an increasing number of clinical trials using CT-MSCs as the primary source of regeneration are underway. A routine search on the FDA's link clinicaltrials.gov reveals no less than 54 registered clinical studies which employ CT-MSCs as the primary study drug as of July 2013.

MSCs have been shown in numerous independent studies to have the capacity to differentiate into bone[39], nerve[40], muscle[41], and endocrine[42] phenotypes, regulate immune responses[43], and functionally repair or reconstitute relevant animal models of disease[44].

Although the relevance of these studies is yet to be determined, the intended uses are broad and include: Autism (1), Respiratory (4), Wound Healing (2), Cardio-vascular (3), Diabetes Mellitus and other Autoimmune diseases (8), Gastro-enterologic (1), Hematologic (6), Infectious Disease (1), Liver (12), Muscle (1), Kidney (1), Vascular (1), Neurodegenerative (8), Fertility (2) and Orthopedic (3).[45]

To be clear, none of these referenced studies have been designed for the use of a child's own CT-MSCs for themselves or a family member, but this is primarily because the inventory of CT-MSCs is relatively small and the age of children who banked is relatively young. As the inventory, health history, and the purported clinical utility matures, this is likely to change dramatically.

More than just a Spare Tire—Co-Administration: CBSCs + CT-MSCs

CBSC transplants are now established medical practice. Over 30,000 CB transplants have been performed and 22% of all transplants are now done using this source of stem cells.[46] This is largely due to the immediate availability of stored units in the public banking inventory and relaxed matching criteria which result in higher probabilities of finding an adequate match lower rates of Graft versus Host Disease when compared with Bone Marrow. Clinical reports have now established that the long-term outcomes of transplants, as measured by survival, are roughly equivalent. Importantly, more patients die in the first 100 days after CB transplants due to a slower rate of engraftment, while more die from GvHD after the first 100 days following BM transplants.[47] One explanation for the difference in engraftment rates is the presence of adult-MSCs in BM which have been proposed to hasten engraftment through a variety of mechanisms including the facilitation of stem cell homing, secretion of stem cell supportive paracrine factors, repair and regeneration of auxiliary tissues such as the mucosal lining and gut damaged by harsh treatment regimens, and cell-cell nursing functions specific to the stem cell niche. Using multiple avenues of exploration, empirical evidence is quickly gathering to support this important proposition. The co-culture strategy was first employed by McNiece[48] and then Laughlin[49] in *in vitro* proof of principle experiments. Taghizadeh et al demonstrated in 2010 a six-fold enhancement in the number of donor human cells found in mice eight weeks after transplantation as compared to controls without CT-MSCs.[50] Since that point two clinical studies have been reported where MSCs were used to augment clinical transplantation: Schpall et al, demonstrated that the co-culture of CBSCs with haploidentical MSCs reduced time to engraftment to 14.5 days[51], reinforcing the notion that MSCs play an important nursing function in the CBSC niche, and Wu et al. utilized the co-administration of MSCs derived from cord tissue and CBSCs to achieve a nearly 3-fold reduction in the median time to engraftment

(11 days versus 32 days).[52] As a reminder, delayed engraftment correlates strongly with higher rates of morbidity and mortality, while improved engraftment translates into better outcomes with respect to survival.[53]

Other applications of note where a bollus of CT-MSCs may augment the use of CBSCs include both Cerebral Palsy (CP) and Type 1 Diabetes. In the case of CP, where direct intravenous infusions in the absence of chemotherapeutic treatment is currently being evaluated, there is some expectation that in addition to paracine effects on vessel formation or neural regeneration[54], component cells in cord blood similar to CT-MSCs but called Unrestricted Somatic Stem Cells (or USSCs)[55], may cross the blood brain barrier and form neural components. Unfortunately, the frequency of native USSCs in CB is marginal at best, with the isolation of 1-11 proliferative colony-forming clones restricted to less than half of all fresh cord blood units.[56]

The prospect of enhancing CBSC treatments in Cerebal Palsy with millions of CT-MSC isolated per gram of CT holds tremendous promise given both the angiogenic properties[57] and the neuroregenerative potential of these cells. Supporting this approach, Ding, et al. reported that following the transplant of human CT-MSCs into the cortex of rats having received focal damage to the brain by 90-minute ligation of the middle cerebral artery, the subject animals demonstrated improvement in motor asymmetry relative to controls. Differentiation of CT-MSCs into neural, vascular and microglial phenotypes, along with the formation of new blood vessels in the ischemic area, were also observed.[58] Employing a similar stroke model, subject animals having received induced infarcts and CT-MSCs showed significant reductions in the volume of infarct volume relative to controls, concomitant with improvements in motor neuron composite scores that included motor, sensory, balance and reflex tests.[59] The directed differentiation of CT-MSCs into neural components *in vitro* has also been demonstrated through the use of exogenous neural factors.[60]

In the case of Type 1 Diabetes, the working hypothesis for autologous CBSC treatment is the opportunity for introducing newborn T-regulatory cells present in the CB specimen.[61] These T-regs may assist in adjusting imbalances resulting from autoimmunity, albeit only temporarily, although sufficient numbers of children with T1D have not yet been treated to document a significant clinical improvement. This could be for a number of reasons including the fact that children entering the study have well established disease, perhaps intractable with a limited number of T-regs. Enhancements of this strategy include expansion of T-regs from a portion of the CBSC unit, so that multiple or even ongoing infusions can be provided. How might CT-MSCs augment this strategy? By the time a patient is diagnosed with T1D, 50-80% of the beta-cell reservoire has already degenerated, presenting a life-long challenge even if the autoimmune component of the disease can be kept at bay. Different from CBSCs and T-reg cells, the CT-MSCs fraction has been shown to possess the ability to successfully differentiate into mature islet-like cell clusters with insulin-producing ablity[62], opening the possibility of further organ regeneration following attenuation of autoimmune-driven disease processes.

Who's Borrowing the Keys to the Family Car Now: Or, Why CT-MSCs May Not be Just for Junior

CT-MSCs present an intriguing matching paradigm which is quite different from the CBSCs transplant paradigm, where HLA matching must be a minimum of 4/6 and preferably 6/6 and autologous regeneration where exact matches are achievable (See Figure 8, Panel A). Unlike CBSCs which can cause Graft versus Host Disease (GVHD), CT-MSCs do not differentiate into cells of the immune system, but do possess immune regulatory properties as well as tissue-specific regenerative potential. This makes CT-MSCs an excellent source of stem cells for either transient

Figure 8, Panel A: The Cord Blood Transplant Paradigm is predicated on maximizing matching criteria (preferably 6/6 HLA matches). This is because mismatched donor transplant grafts can cause GvHD in recipients leading to significant morbidity and mortality, and because new applications of regenerative medicine using a child's own cord blood to treat an acquired disease, where immune suppression is not a feature of the treatment, may require a perfect self-matched or autologous unit.

Figure 8, Panel B: The Cord Tissue Regeneration Paradigm is predicated on minimum matching criteria (i.e. haploidentical), as regeneration requires that the host's competent immune system not reject the graft (i.e., in this case, HvGD not GvHD). For this reason, there is a high likelihood that biological family members are haploidentical, including a 75% chance for siblings, 100% chance for parents and 25% for grandparents. Given this and the multiple indications for MSCs in a broad class of diseases, both the potential utility and probability of use of CT-MSCs for immediate family members is extended well beyond the current and future Cord Blood Paradigm (Panel A).

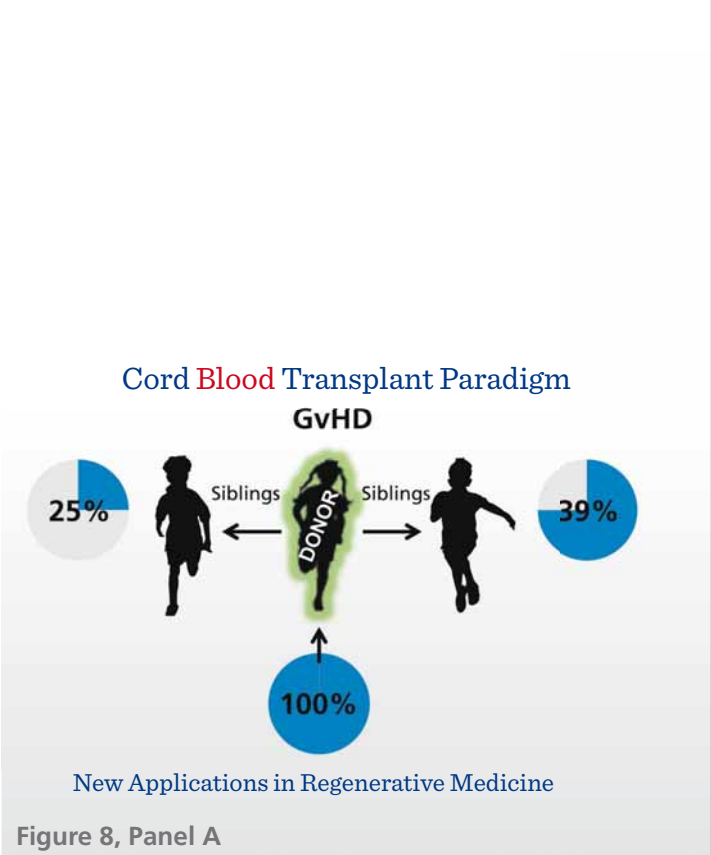
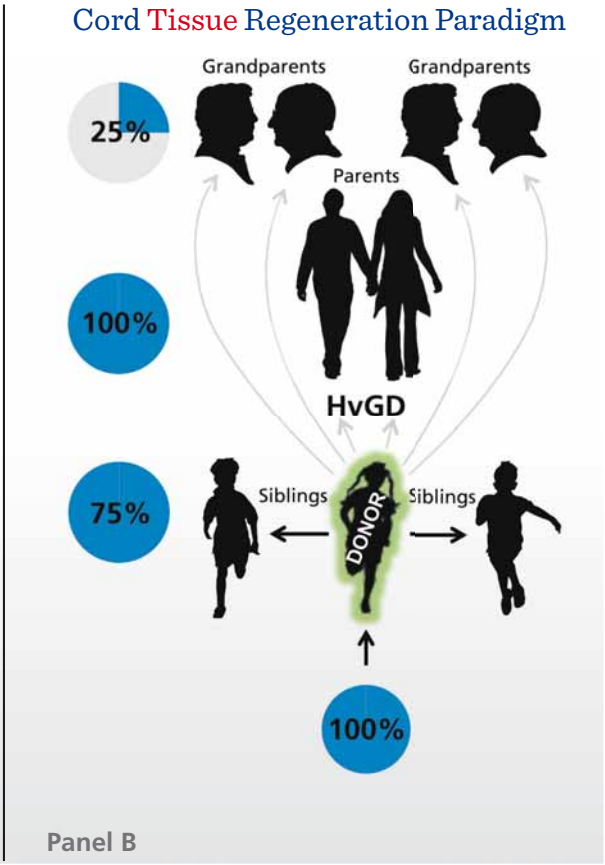


Figure 8, Panel A



Panel B

immune regulation in unmatched allogeneic applications or tissue regeneration in matched haploidentical recipients, representing an entirely different matching paradigm. Haploidentical matching may be critical in the application of CT-MSCs in regenerative medicine since downstream tissue integration using Human Leukocyte (HLA) Class II negative precursor stem cells, which can avoid immune rejection, may result in tissue-specific differentiated cells expressing Class II antigens, which would be detected by the host's intact immune system and ultimately rejected.[63] (See Figure 8, Panel B)

For this reason, it is widely believed that the application of primary CT-MSCs, those that have not been expanded in culture, for regenerative medicine will require haploidentical donors.

For this reason, it is widely believed that the application of primary CT-MSCs, those that have not been expanded in culture, for regenerative medicine will require haploidentical donors. Since haplotypes are inherited from ones' biological parents, each child's CT-MSCs are sufficiently well-matched, i.e. a minimum of haploidentical, to avoid Host versus Graft Disease (HVGD), or the rejection of the donor cells by the host. Biological siblings would be sufficiently matched seventy-five percent of the time, i.e. including both haploidenticals (75%) and identicals (25%). Furthermore, biological grandparents are predicted to be haploidentical with any one of their grandchildren 25% of the time.[64] Assuming haploidentical matching is indeed the minimum requirement for regenerative therapies, the potential to use this source of newborn stem cells generationally would directly map to a large variety of autoimmune and degenerative disease indications within the family tree, including Rheumatoid Arthritis[65], Diabetes[66], Stroke[67], Parkinson's[68], Chronic Heart Failure[69], Liver Fibrosis[70], and perhaps many others. Access to a family source of newborn CT-MSCs, therefore, may have profound implications.

Taking the Wheel: Preparing for the Regenerative Medicine Journey

According to a recent survey 72% of practicing physicians expect stem cell therapy to be a standard therapeutic option within ten years[71] and yet it is doubtful most recognize the relative complexities or risks with respect to this proposition. As CBSCs and CT-MSCs are both ethically acceptable, relatively naïve, multipotent cells, it is likely this unique resource will serve as a primary raw material for multiple therapeutic formulations with regenerative properties. Families should be keenly aware of this before CBSC or CT-MSCs are discarded as mere medical waste, as the arrival of a newborn in the arc of one's family history may represent the best opportunity to preserve access to this very powerful biology.

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